Inhaltsverzeichnis

Subgruppenanalysen zum Endpunkt „Veränderung der polyneuropathischen Symptomatik gemessen anhand des mNIS+7“

mNIS+7-Gesamtwert (Kontinuierliche Analyse)

Alnylam Pharmaceuticals Inc.
ALN-TTRSC02-002

Table 2.5
Modified Neuropathy Impairment Score +7 (mNIS+7): Change from Baseline to Month 18, MMRM Model
Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A) Subgroup Analysis
mITT Population

Subgroup Visit	LS Mean (95% CI) Vutrisiran (HELIOS-A) (N=122)	LS Mean (95% CI) Patisiran (HELIOS-A) (N=42)	LS Mean Difference (Vutrisiran-Patisiran) (95% CI), p-value	Standardized Effect Size (95% CI)
Age (years)				
<65	75	30		
Month 9	-2.42 (-5.65, 0.82)	1.22 (-3.92, 6.37)	-3.64 (-9.71, 2.43), 0.2384	-0.26 (-0.68, 0.16)
Month 18	-0.46 (-4.05, 3.12)	3.16 (-2.75, 9.08)	-3.63 (-10.54, 3.29), 0.3020	-0.20 (-0.64, 0.24)
≥65	44	10		
Month 9	0.87 (-3.33, 5.07)	-5.33 (-14.09, 3.42)	6.20 (-3.51, 15.91), 0.2088	0.41 (-0.27, 1.10)
Month 18	2.82 (-1.66, 7.31)	-3.39 (-12.61, 5.83)	6.21 (-4.03, 16.46), 0.2331	0.48 (-0.24, 1.20)
p-value of Treatment*Age	0.0883			

mNIS+7 score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurologic impairment (range = 0 to 304). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.
LS estimates and p-value derived from mixed-effects model for repeated measures (MMRM), controlling for categorical factors (treatment, visit), the subgroup variable, continuous covariate (baseline value), and interaction (treatment by visit, treatment by subgroup).
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Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

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mITT Population

Subgroup Visit	LS Mean (95% CI) Vutrisiran (HELIOS-A) (N=122)	LS Mean (95% CI) Patisiran (HELIOS-A) (N=42)	LS Mean Difference (Vutrisiran-Patisiran) (95% CI), p-value	Standardized Effect Size (95% CI)
Sex				
Male	77	25		
Month 9	0.37 (-2.83, 3.58)	0.31 (-5.28, 5.91)	0.06 (-6.39, 6.52), 0.9849	0.00 (-0.44, 0.45)
Month 18	2.33 (-1.25, 5.91)	2.26 (-4.09, 8.60)	0.07 (-7.23, 7.38), 0.9839	0.00 (-0.47, 0.48)
Female	42	15		
Month 9	-4.11 (-8.43, 0.20)	-1.74 (-8.91, 5.43)	-2.37 (-10.73, 5.98), 0.5758	-0.14 (-0.73, 0.44)
Month 18	-2.16 (-6.75, 2.43)	0.20 (-7.54, 7.94)	-2.36 (-11.35, 6.63), 0.6051	-0.12 (-0.72, 0.48)
p-value of Treatment*Sex	0.6458			

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mITT Population

Subgroup Visit	LS Mean (95% CI) Vutrisiran (HELIOS-A) (N=122)	LS Mean (95% CI) Patisiran (HELIOS-A) (N=42)	LS Mean Difference (Vutrisiran-Patisiran) (95% CI), p-value	Standardized Effect Size (95% CI)
Race				
White	84	28		
Month 9	-1.12 (-4.20, 1.96)	1.33 (-3.99, 6.65)	-2.45 (-8.60, 3.70), 0.4321	-0.17 (-0.59, 0.26)
Month 18	0.83 (-2.63, 4.28)	3.28 (-2.80, 9.35)	-2.45 (-9.44, 4.54), 0.4899	-0.14 (-0.59, 0.30)
All Other Races	35	12		
Month 9	-1.41 (-6.14, 3.32)	-4.57 (-12.65, 3.51)	3.16 (-6.21, 12.53), 0.5063	0.23 (-0.42, 0.88)
Month 18	0.54 (-4.44, 5.52)	-2.62 (-11.20, 5.96)	3.16 (-6.77, 13.09), 0.5306	0.21 (-0.47, 0.88)
p-value of Treatment*Race	0.3185			

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mITT Population

Subgroup Visit	LS Mean (95% CI) Vutrisiran (HELIOS-A) (N=122)	LS Mean (95% CI) Patisiran (HELIOS-A) (N=42)	LS Mean Difference (Vutrisiran-Patisiran) (95% CI), p-value	Standardized Effect Size (95% CI)
Region				
North America	27	8		
Month 9	-7.07 (-12.69, -1.46)	-7.03 (-16.79, 2.74)	-0.05 (-11.18, 11.08), 0.9931	-0.00 (-0.78, 0.77)
Month 18	-5.09 (-10.86, 0.69)	-5.15 (-15.37, 5.06)	0.07 (-11.53, 11.66), 0.9909	0.01 (-0.86, 0.87)
Western Europe	40	18		
Month 9	0.01 (-4.33, 4.36)	-0.72 (-7.23, 5.80)	0.73 (-7.10, 8.57), 0.8538	0.05 (-0.50, 0.60)
Month 18	2.00 (-2.58, 6.59)	1.15 (-5.89, 8.20)	0.85 (-7.56, 9.25), 0.8424	0.07 (-0.49, 0.63)
Rest of World	52	14		
Month 9	0.82 (-3.10, 4.74)	3.33 (-4.04, 10.70)	-2.51 (-10.89, 5.87), 0.5550	-0.16 (-0.75, 0.42)
Month 18	2.80 (-1.39, 7.00)	5.20 (-2.65, 13.04)	-2.39 (-11.33, 6.54), 0.5977	-0.11 (-0.71, 0.49)
p-value of Treatment*Region	0.8465			

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mITT Population

Subgroup Visit	LS Mean (95% CI) Vutrisiran (HELIOS-A) (N=122)	LS Mean (95% CI) Patisiran (HELIOS-A) (N=42)	LS Mean Difference (Vutrisiran-Patisiran) (95% CI), p-value	Standardized Effect Size (95% CI)
Baseline NIS				
<50	77	27		
Month 9	-4.17 (-7.86, -0.47)	-4.16 (-9.87, 1.55)	-0.01 (-6.22, 6.21), 0.9984	-0.00 (-0.44, 0.43)
Month 18	-2.22 (-6.21, 1.76)	-2.21 (-8.55, 4.14)	-0.01 (-6.98, 6.95), 0.9966	-0.00 (-0.45, 0.45)
≥50	42	13		
Month 9	4.36 (-1.22, 9.94)	6.01 (-2.11, 14.13)	-1.65 (-10.44, 7.13), 0.7107	-0.10 (-0.71, 0.52)
Month 18	6.30 (0.54, 12.07)	7.97 (-0.64, 16.57)	-1.66 (-11.02, 7.69), 0.7264	-0.08 (-0.74, 0.58)
p-value of Treatment*Baseline NIS	0.7594			

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mITT Population

Subgroup Visit	LS Mean (95% CI) Vutrisiran (HELIOS-A) (N=122)	LS Mean (95% CI) Patisiran (HELIOS-A) (N=42)	LS Mean Difference (Vutrisiran-Patisiran) (95% CI), p-value	Standardized Effect Size (95% CI)
Previous Tetramer Stabilizer Use				
Yes	74	32		
Month 9	-3.09 (-6.34, 0.16)	0.16 (-4.79, 5.11)	-3.25 (-9.17, 2.68), 0.2807	-0.22 (-0.63, 0.20)
Month 18	-1.17 (-4.80, 2.46)	2.10 (-3.66, 7.86)	-3.27 (-10.08, 3.54), 0.3450	-0.18 (-0.61, 0.25)
No	45	8		
Month 9	1.95 (-2.24, 6.14)	-2.60 (-12.44, 7.24)	4.55 (-6.09, 15.18), 0.3996	0.36 (-0.38, 1.11)
Month 18	3.87 (-0.59, 8.32)	-0.66 (-10.94, 9.62)	4.53 (-6.62, 15.67), 0.4240	0.35 (-0.44, 1.14)
p-value of Treatment*Previous Tetramer Stabilizer Use	0.2029			

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mITT Population

Subgroup Visit	LS Mean (95% CI) Vutrisiran (HELIOS-A) (N=122)	LS Mean (95% CI) Patisiran (HELIOS-A) (N=42)	LS Mean Difference (Vutrisiran-Patisiran) (95% CI), p-value	Standardized Effect Size (95% CI)
Genotype				
V30M	53	20		
Month 9	-1.36 (-5.24, 2.51)	-1.63 (-7.92, 4.67)	0.26 (-7.12, 7.65), 0.9442	0.02 (-0.49, 0.53)
Month 18	0.58 (-3.58, 4.75)	0.33 (-6.56, 7.22)	0.25 (-7.79, 8.30), 0.9503	0.02 (-0.50, 0.54)
non-V30M	66	20		
Month 9	-1.08 (-4.56, 2.40)	0.80 (-5.54, 7.14)	-1.88 (-9.09, 5.34), 0.6084	-0.12 (-0.61, 0.38)
Month 18	0.87 (-2.94, 4.68)	2.75 (-4.24, 9.75)	-1.88 (-9.83, 6.07), 0.6408	-0.10 (-0.63, 0.44)
p-value of Treatment*Genotype	0.6788			

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mITT Population

Subgroup Visit	LS Mean (95% CI) Vutrisiran (HELIOS-A) (N=122)	LS Mean (95% CI) Patisiran (HELIOS-A) (N=42)	LS Mean Difference (Vutrisiran-Patisiran) (95% CI), p-value	Standardized Effect Size (95% CI)
FAP Stage				
I	83	30		
Month 9	-3.06 (-6.22, 0.11)	-0.59 (-5.83, 4.65)	-2.47 (-8.44, 3.51), 0.4164	-0.18 (-0.59, 0.24)
Month 18	-1.10 (-4.63, 2.42)	1.34 (-4.61, 7.29)	-2.44 (-9.23, 4.35), 0.4789	-0.14 (-0.56, 0.28)
II&III	36	10		
Month 9	3.10 (-1.86, 8.07)	-0.47 (-9.47, 8.54)	3.57 (-6.34, 13.47), 0.4777	0.23 (-0.46, 0.93)
Month 18	5.06 (-0.15, 10.26)	1.47 (-8.09, 11.02)	3.59 (-6.92, 14.11), 0.5013	0.24 (-0.56, 1.04)
p-value of Treatment*FAP Stage	0.3004			

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mITT Population

Subgroup Visit	LS Mean (95% CI) Vutrisiran (HELIOS-A) (N=122)	LS Mean (95% CI) Patisiran (HELIOS-A) (N=42)	LS Mean Difference (Vutrisiran-Patisiran) (95% CI), p-value	Standardized Effect Size (95% CI)
Cardiac Subpopulation				
Yes	38	14		
Month 9	2.36 (-2.06, 6.78)	8.67 (1.48, 15.87)	-6.31 (-14.74, 2.12), 0.1410	-0.43 (-1.04, 0.18)
Month 18	4.33 (-0.35, 9.01)	10.57 (2.86, 18.29)	-6.24 (-15.25, 2.76), 0.1731	-0.29 (-0.91, 0.34)
No	81	26		
Month 9	-2.89 (-5.95, 0.16)	-5.47 (-10.83, -0.11)	2.58 (-3.56, 8.72), 0.4083	0.19 (-0.25, 0.63)
Month 18	-0.93 (-4.33, 2.48)	-3.57 (-9.65, 2.50)	2.65 (-4.29, 9.58), 0.4520	0.20 (-0.26, 0.67)
p-value of Treatment*Cardiac Subpopulation	0.0890			

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Weight (kg)				
<65	44	15		
Month 9	-1.37 (-5.66, 2.93)	2.96 (-4.26, 10.17)	-4.32 (-12.75, 4.10), 0.3123	-0.32 (-0.90, 0.26)
Month 18	0.58 (-4.01, 5.17)	4.91 (-2.89, 12.71)	-4.33 (-13.41, 4.74), 0.3474	-0.22 (-0.84, 0.39)
≥65	75	25		
Month 9	-1.11 (-4.41, 2.19)	-2.45 (-8.08, 3.18)	1.34 (-5.16, 7.84), 0.6838	0.09 (-0.36, 0.54)
Month 18	0.84 (-2.80, 4.48)	-0.50 (-6.83, 5.84)	1.33 (-5.95, 8.61), 0.7182	0.09 (-0.38, 0.55)
p-value of Treatment*Weight	0.2894			

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Table 2.7
Modified Neuropathy Impairment Score +7 (mNIS+7): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Age (years): <65

Subgroup Visit	Vutrisiran (HELIOS-A) (N=76)	Patisiran (HELIOS-A) (N=31)
Baseline		
n	76	31
Mean (SD)	59.18 (35.98)	53.60 (29.34)
SE	4.13	5.27
Median	60.19	52.50
Min, Max	2.5, 158.0	7.0, 116.4
Month 9		
Actual Value		
n	74	30
Mean (SD)	55.70 (37.76)	53.13 (35.12)
SE	4.39	6.41
Median	53.50	50.38
Min, Max	1.0, 160.1	6.0, 152.3
Change from baseline		
n	74	30
Mean (SD)	-2.50 (13.22)	1.22 (15.68)
SE	1.54	2.86
Median	-0.25	-2.00
Min, Max	-35.0, 25.5	-29.0, 62.9

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mITT Population

Age (years): <65

Subgroup Visit	Vutrisiran (HELIOS-A) (N=76)	Patisiran (HELIOS-A) (N=31)
Month 18		
Actual Value		
n	74	27
Mean (SD)	58.33 (39.64)	52.14 (38.36)
SE	4.61	7.38
Median	52.88	40.00
Min, Max	1.0, 164.8	8.5, 167.9
Change from baseline		
n	74	27
Mean (SD)	-0.26 (15.99)	3.48 (23.45)
SE	1.86	4.51
Median	-1.00	1.50
Min, Max	-37.8, 59.0	-26.5, 106.1

mNIS+7 score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurologic impairment (range = 0 to 304). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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mITT Population

Age (years): ≥65

Subgroup Visit	Vutrisiran (HELIOS-A) (N=46)	Patisiran (HELIOS-A) (N=11)
Baseline		
n	46	11
Mean (SD)	62.87 (36.29)	69.16 (43.35)
SE	5.35	13.07
Median	68.25	62.00
Min, Max	5.0, 135.5	13.0, 137.6
Month 9		
Actual Value		
n	43	10
Mean (SD)	62.47 (38.03)	59.39 (43.46)
SE	5.80	13.74
Median	64.50	53.00
Min, Max	4.0, 135.6	7.0, 153.5
Change from baseline		
n	43	10
Mean (SD)	0.95 (13.17)	-5.29 (21.36)
SE	2.01	6.75
Median	-0.50	0.55
Min, Max	-27.4, 26.0	-47.0, 24.0

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mITT Population

Age (years): ≥65

Subgroup Visit	Vutrisiran (HELIOS-A) (N=46)	Patisiran (HELIOS-A) (N=11)
Month 18		
Actual Value		
n	41	9
Mean (SD)	64.98 (41.63)	63.84 (38.82)
SE	6.50	12.94
Median	72.38	58.50
Min, Max	1.0, 145.6	13.0, 141.5
Change from baseline		
n	41	9
Mean (SD)	3.04 (12.70)	-4.08 (13.70)
SE	1.98	4.57
Median	1.50	-3.50
Min, Max	-21.0, 41.4	-30.4, 15.0

mNIS+7 score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurologic impairment (range = 0 to 304). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

Alnylam Pharmaceuticals Inc.
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Table 2.7
Modified Neuropathy Impairment Score +7 (mNIS+7): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Sex: Male

Subgroup Visit	Vutrisiran (HELIOS-A) (N=79)	Patisiran (HELIOS-A) (N=27)
Baseline		
n	79	27
Mean (SD)	64.19 (35.85)	58.69 (32.19)
SE	4.03	6.19
Median	66.00	61.50
Min, Max	3.0, 158.0	8.0, 116.4
Month 9		
Actual Value		
n	76	25
Mean (SD)	63.80 (38.56)	55.12 (34.16)
SE	4.42	6.83
Median	63.75	63.00
Min, Max	3.5, 160.1	6.0, 152.3
Change from baseline		
n	76	25
Mean (SD)	0.55 (12.99)	0.48 (13.00)
SE	1.49	2.60
Median	1.07	-0.25
Min, Max	-35.0, 23.5	-26.4, 35.9

mNIS+7 score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurologic impairment (range = 0 to 304). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Alnylam Pharmaceuticals Inc.
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Table 2.7
Modified Neuropathy Impairment Score +7 (mNIS+7): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Sex: Male

Subgroup Visit	Vutrisiran (HELIOS-A) (N=79)	Patisiran (HELIOS-A) (N=27)
Month 18		
Actual Value		
n	74	22
Mean (SD)	65.00 (41.48)	55.03 (30.05)
SE	4.82	6.41
Median	66.38	58.75
Min, Max	1.0, 164.8	10.0, 137.4
Change from baseline		
n	74	22
Mean (SD)	2.06 (15.82)	1.94 (11.62)
SE	1.84	2.48
Median	-0.13	2.25
Min, Max	-26.0, 59.0	-30.4, 25.0

mNIS+7 score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurologic impairment (range = 0 to 304). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Alnylam Pharmaceuticals Inc.
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Table 2.7
Modified Neuropathy Impairment Score +7 (mNIS+7): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Sex: Female

Subgroup Visit	Vutrisiran (HELIOS-A) (N=43)	Patisiran (HELIOS-A) (N=15)
Baseline		
n	43	15
Mean (SD)	53.92 (35.71)	55.85 (37.39)
SE	5.45	9.65
Median	48.50	52.50
Min, Max	2.5, 140.6	7.0, 137.6
Month 9		
Actual Value		
n	41	15
Mean (SD)	47.80 (34.54)	53.98 (42.30)
SE	5.39	10.92
Median	44.38	50.00
Min, Max	1.0, 116.3	7.0, 153.5
Change from baseline		
n	41	15
Mean (SD)	-4.54 (13.25)	-1.88 (23.06)
SE	2.07	5.95
Median	-4.00	-2.00
Min, Max	-29.5, 26.0	-47.0, 62.9

mNIS+7 score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurologic impairment (range = 0 to 304). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Alnylam Pharmaceuticals Inc.
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Table 2.7
Modified Neuropathy Impairment Score +7 (mNIS+7): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Sex: Female

Subgroup Visit	Vutrisiran (HELIOS-A) (N=43)	Patisiran (HELIOS-A) (N=15)
Month 18		
Actual Value		
n	41	14
Mean (SD)	52.94 (37.34)	55.12 (49.82)
SE	5.83	13.32
Median	47.25	35.00
Min, Max	4.0, 129.4	8.5, 167.9
Change from baseline		
n	41	14
Mean (SD)	-1.15 (13.10)	1.03 (32.04)
SE	2.05	8.56
Median	-1.00	-3.19
Min, Max	-37.8, 26.0	-26.5, 106.1

mNIS+7 score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurologic impairment (range = 0 to 304). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Alnylam Pharmaceuticals Inc.
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Table 2.7
Modified Neuropathy Impairment Score +7 (mNIS+7): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Race: White

Subgroup Visit	Vutrisiran (HELIOS-A) (N=86)	Patisiran (HELIOS-A) (N=29)
Baseline		
n	86	29
Mean (SD)	59.77 (35.42)	60.40 (32.31)
SE	3.82	6.00
Median	63.50	54.38
Min, Max	2.5, 140.6	7.0, 137.6
Month 9		
Actual Value		
n	83	28
Mean (SD)	57.80 (37.23)	59.93 (38.32)
SE	4.09	7.24
Median	63.00	56.75
Min, Max	1.0, 137.5	7.0, 153.5
Change from baseline		
n	83	28
Mean (SD)	-1.15 (12.64)	1.44 (19.58)
SE	1.39	3.70
Median	-0.38	0.00
Min, Max	-35.0, 25.5	-47.0, 62.9

mNIS+7 score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurologic impairment (range = 0 to 304). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Alnylam Pharmaceuticals Inc.
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Table 2.7
Modified Neuropathy Impairment Score +7 (mNIS+7): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Race: White

Subgroup Visit	Vutrisiran (HELIOS-A) (N=86)	Patisiran (HELIOS-A) (N=29)
Month 18		
Actual Value		
n	82	25
Mean (SD)	60.21 (39.19)	59.04 (41.39)
SE	4.33	8.28
Median	61.06	47.00
Min, Max	1.0, 145.6	8.5, 167.9
Change from baseline		
n	82	25
Mean (SD)	0.91 (14.92)	3.25 (23.75)
SE	1.65	4.75
Median	-1.50	0.00
Min, Max	-37.8, 59.0	-24.5, 106.1

mNIS+7 score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurologic impairment (range = 0 to 304). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 2.7
Modified Neuropathy Impairment Score +7 (mNIS+7): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Race: All Other Races

Subgroup Visit	Vutrisiran (HELIOS-A) (N=36)	Patisiran (HELIOS-A) (N=13)
Baseline		
n	36	13
Mean (SD)	62.49 (37.77)	51.60 (37.26)
SE	6.30	10.34
Median	59.06	40.00
Min, Max	3.5, 158.0	8.0, 115.9
Month 9		
Actual Value		
n	34	12
Mean (SD)	59.14 (39.83)	42.47 (31.40)
SE	6.83	9.07
Median	51.50	42.94
Min, Max	7.0, 160.1	6.0, 89.5
Change from baseline		
n	34	12
Mean (SD)	-1.43 (14.83)	-4.71 (8.98)
SE	2.54	2.59
Median	-0.63	-4.00
Min, Max	-28.5, 26.0	-26.4, 12.0

mNIS+7 score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurologic impairment (range = 0 to 304). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Alnylam Pharmaceuticals Inc.
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Table 2.7
Modified Neuropathy Impairment Score +7 (mNIS+7): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Race: All Other Races

Subgroup Visit	Vutrisiran (HELIOS-A) (N=36)	Patisiran (HELIOS-A) (N=13)
Month 18		
Actual Value		
n	33	11
Mean (SD)	61.93 (43.56)	46.04 (29.72)
SE	7.58	8.96
Median	48.50	35.00
Min, Max	4.0, 164.8	10.0, 88.6
Change from baseline		
n	33	11
Mean (SD)	0.92 (15.18)	-2.20 (15.57)
SE	2.64	4.69
Median	2.50	2.00
Min, Max	-26.5, 50.6	-30.4, 25.0

mNIS+7 score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurologic impairment (range = 0 to 304). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 2.7
Modified Neuropathy Impairment Score +7 (mNIS+7): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Region: North America

Subgroup Visit	Vutrisiran (HELIOS-A) (N=27)	Patisiran (HELIOS-A) (N=8)
Baseline		
n	27	8
Mean (SD)	35.47 (30.82)	46.05 (22.52)
SE	5.93	7.96
Median	28.00	47.58
Min, Max	2.5, 119.0	7.0, 80.5
Month 9		
Actual Value		
n	25	8
Mean (SD)	23.40 (18.25)	41.11 (23.25)
SE	3.65	8.22
Median	19.00	39.25
Min, Max	1.0, 79.0	7.0, 74.5
Change from baseline		
n	25	8
Mean (SD)	-6.11 (12.50)	-4.95 (10.90)
SE	2.50	3.85
Median	-1.50	-1.00
Min, Max	-35.0, 22.0	-29.0, 6.5

mNIS+7 score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurologic impairment (range = 0 to 304). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 2.7
Modified Neuropathy Impairment Score +7 (mNIS+7): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Region: North America

Subgroup Visit	Vutrisiran (HELIOS-A) (N=27)	Patisiran (HELIOS-A) (N=8)
Month 18		
Actual Value		
n	25	6
Mean (SD)	29.98 (33.53)	31.47 (17.16)
SE	6.71	7.01
Median	19.00	33.25
Min, Max	1.0, 120.0	8.5, 59.3
Change from baseline		
n	25	6
Mean (SD)	-5.47 (8.90)	-10.60 (10.50)
SE	1.78	4.29
Median	-3.00	-11.80
Min, Max	-26.0, 8.1	-24.5, 1.5

mNIS+7 score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurologic impairment (range = 0 to 304). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 2.7
Modified Neuropathy Impairment Score +7 (mNIS+7): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Region: Western Europe

Subgroup Visit	Vutrisiran (HELIOS-A) (N=42)	Patisiran (HELIOS-A) (N=20)
Baseline		
n	42	20
Mean (SD)	61.48 (32.75)	64.15 (34.94)
SE	5.05	7.81
Median	64.38	61.75
Min, Max	8.0, 131.9	13.0, 137.6
Month 9		
Actual Value		
n	40	18
Mean (SD)	61.08 (32.86)	58.67 (35.08)
SE	5.20	8.27
Median	63.25	64.38
Min, Max	4.0, 129.3	7.0, 153.5
Change from baseline		
n	40	18
Mean (SD)	0.16 (13.95)	-0.47 (15.52)
SE	2.20	3.66
Median	-0.06	1.75
Min, Max	-30.6, 26.0	-47.0, 24.0

mNIS+7 score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurologic impairment (range = 0 to 304). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

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Table 2.7
Modified Neuropathy Impairment Score +7 (mNIS+7): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Region: Western Europe

Subgroup Visit	Vutrisiran (HELIOS-A) (N=42)	Patisiran (HELIOS-A) (N=20)
Month 18		
Actual Value		
n	40	17
Mean (SD)	62.46 (34.24)	58.09 (32.66)
SE	5.41	7.92
Median	63.38	58.50
Min, Max	6.0, 129.4	11.0, 141.5
Change from baseline		
n	40	17
Mean (SD)	1.54 (13.35)	0.28 (7.84)
SE	2.11	1.90
Median	-0.13	0.00
Min, Max	-37.8, 27.5	-16.8, 15.0

mNIS+7 score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurologic impairment (range = 0 to 304). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 2.7
Modified Neuropathy Impairment Score +7 (mNIS+7): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Region: Rest of World

Subgroup Visit	Vutrisiran (HELIOS-A) (N=53)	Patisiran (HELIOS-A) (N=14)
Baseline		
n	53	14
Mean (SD)	72.63 (34.89)	55.07 (37.04)
SE	4.79	9.90
Median	76.38	55.69
Min, Max	3.5, 158.0	8.0, 116.4
Month 9		
Actual Value		
n	52	14
Mean (SD)	72.69 (38.20)	57.34 (45.15)
SE	5.30	12.07
Median	77.31	51.13
Min, Max	7.0, 160.1	6.0, 152.3
Change from baseline		
n	52	14
Mean (SD)	0.04 (12.74)	2.27 (22.13)
SE	1.77	5.91
Median	1.50	-4.56
Min, Max	-28.0, 25.5	-26.4, 62.9

mNIS+7 score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurologic impairment (range = 0 to 304). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 2.7
Modified Neuropathy Impairment Score +7 (mNIS+7): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Region: Rest of World

Subgroup Visit	Vutrisiran (HELIOS-A) (N=53)	Patisiran (HELIOS-A) (N=14)
Month 18		
Actual Value		
n	50	13
Mean (SD)	74.66 (40.16)	62.00 (48.79)
SE	5.68	13.53
Median	80.00	53.88
Min, Max	4.0, 164.8	10.0, 167.9
Change from baseline		
n	50	13
Mean (SD)	3.61 (17.58)	8.92 (32.95)
SE	2.49	9.14
Median	2.81	3.00
Min, Max	-26.5, 59.0	-30.4, 106.1

mNIS+7 score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurologic impairment (range = 0 to 304). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 2.7
Modified Neuropathy Impairment Score +7 (mNIS+7): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Baseline NIS: <50

Subgroup Visit	Vutrisiran (HELIOS-A) (N=78)	Patisiran (HELIOS-A) (N=27)
Baseline		
n	78	27
Mean (SD)	40.12 (24.18)	38.74 (20.66)
SE	2.74	3.98
Median	33.50	36.00
Min, Max	2.5, 92.5	7.0, 80.5
Month 9		
Actual Value		
n	77	27
Mean (SD)	37.93 (26.11)	36.42 (22.60)
SE	2.98	4.35
Median	28.50	36.00
Min, Max	1.0, 105.5	6.0, 74.5
Change from baseline		
n	77	27
Mean (SD)	-1.78 (13.42)	-2.32 (9.04)
SE	1.53	1.74
Median	-0.50	-0.50
Min, Max	-35.0, 26.0	-29.0, 12.0

mNIS+7 score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurologic impairment (range = 0 to 304). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 2.7
Modified Neuropathy Impairment Score +7 (mNIS+7): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Baseline NIS: <50

Subgroup Visit	Vutrisiran (HELIOS-A) (N=78)	Patisiran (HELIOS-A) (N=27)
Month 18		
Actual Value		
n	75	25
Mean (SD)	38.34 (27.61)	37.50 (20.66)
SE	3.19	4.13
Median	30.50	35.00
Min, Max	1.0, 102.3	8.5, 82.6
Change from baseline		
n	75	25
Mean (SD)	-1.48 (14.56)	0.30 (10.32)
SE	1.68	2.06
Median	-2.00	1.50
Min, Max	-37.8, 59.0	-24.5, 25.0

mNIS+7 score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurologic impairment (range = 0 to 304). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 2.7
Modified Neuropathy Impairment Score +7 (mNIS+7): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Baseline NIS: ≥50

Subgroup Visit	Vutrisiran (HELIOS-A) (N=44)	Patisiran (HELIOS-A) (N=15)
Baseline		
n	44	15
Mean (SD)	96.83 (22.23)	91.76 (24.48)
SE	3.35	6.32
Median	92.38	90.13
Min, Max	62.8, 158.0	57.0, 137.6
Month 9		
Actual Value		
n	40	13
Mean (SD)	97.19 (23.66)	92.63 (31.70)
SE	3.74	8.79
Median	93.19	86.00
Min, Max	62.0, 160.1	50.0, 153.5
Change from baseline		
n	40	13
Mean (SD)	-0.18 (13.01)	3.58 (27.58)
SE	2.06	7.65
Median	2.13	-5.00
Min, Max	-27.4, 23.5	-47.0, 62.9

mNIS+7 score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurologic impairment (range = 0 to 304). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 2.7
Modified Neuropathy Impairment Score +7 (mNIS+7): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Baseline NIS: ≥50

Subgroup Visit	Vutrisiran (HELIOS-A) (N=44)	Patisiran (HELIOS-A) (N=15)
Month 18		
Actual Value		
n	40	11
Mean (SD)	102.63 (23.20)	95.00 (39.65)
SE	3.67	11.96
Median	97.50	88.38
Min, Max	67.1, 164.8	30.5, 167.9
Change from baseline		
n	40	11
Mean (SD)	5.41 (14.75)	4.52 (36.73)
SE	2.33	11.07
Median	4.13	-1.75
Min, Max	-23.0, 50.6	-30.4, 106.1

mNIS+7 score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurologic impairment (range = 0 to 304). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 2.7
Modified Neuropathy Impairment Score +7 (mNIS+7): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Previous Tetramer Stabilizer Use: Yes

Subgroup Visit	Vutrisiran (HELIOS-A) (N=75)	Patisiran (HELIOS-A) (N=33)
Baseline		
n	75	33
Mean (SD)	64.70 (36.82)	60.50 (34.13)
SE	4.25	5.94
Median	70.00	61.50
Min, Max	2.5, 158.0	7.0, 137.6
Month 9		
Actual Value		
n	74	32
Mean (SD)	61.40 (38.75)	58.97 (39.05)
SE	4.50	6.90
Median	62.07	64.38
Min, Max	1.0, 160.1	6.0, 153.5
Change from baseline		
n	74	32
Mean (SD)	-3.33 (12.85)	-0.16 (19.17)
SE	1.49	3.39
Median	-1.13	-1.63
Min, Max	-35.0, 25.5	-47.0, 62.9

mNIS+7 score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurologic impairment (range = 0 to 304). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

Alnylam Pharmaceuticals Inc.
ALN-TTRSC02-002

Table 2.7
Modified Neuropathy Impairment Score +7 (mNIS+7): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Previous Tetramer Stabilizer Use: Yes

Subgroup Visit	Vutrisiran (HELIOS-A) (N=75)	Patisiran (HELIOS-A) (N=33)
Month 18		
Actual Value		
n	71	29
Mean (SD)	63.53 (40.08)	60.04 (40.36)
SE	4.76	7.49
Median	61.13	58.50
Min, Max	2.0, 164.8	8.5, 167.9
Change from baseline		
n	71	29
Mean (SD)	-0.16 (15.94)	3.18 (23.41)
SE	1.89	4.35
Median	-2.00	1.50
Min, Max	-37.8, 59.0	-30.4, 106.1

mNIS+7 score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurologic impairment (range = 0 to 304). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

Alnylam Pharmaceuticals Inc.
ALN-TTRSC02-002

Table 2.7
Modified Neuropathy Impairment Score +7 (mNIS+7): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Previous Tetramer Stabilizer Use: No

Subgroup Visit	Vutrisiran (HELIOS-A) (N=47)	Patisiran (HELIOS-A) (N=9)
Baseline		
n	47	9
Mean (SD)	53.98 (33.98)	47.31 (31.78)
SE	4.96	10.59
Median	48.50	51.16
Min, Max	3.0, 119.0	8.0, 114.0
Month 9		
Actual Value		
n	43	8
Mean (SD)	52.66 (35.98)	37.58 (20.27)
SE	5.49	7.17
Median	55.00	39.25
Min, Max	3.5, 133.3	7.5, 67.5
Change from baseline		
n	43	8
Mean (SD)	2.37 (13.30)	-1.40 (4.72)
SE	2.03	1.67
Median	0.63	-1.25
Min, Max	-23.5, 26.0	-10.2, 6.5

mNIS+7 score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurologic impairment (range = 0 to 304). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

Alnylam Pharmaceuticals Inc.
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Table 2.7
Modified Neuropathy Impairment Score +7 (mNIS+7): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Previous Tetramer Stabilizer Use: No

Subgroup Visit	Vutrisiran (HELIOS-A) (N=47)	Patisiran (HELIOS-A) (N=9)
Month 18		
Actual Value		
n	44	7
Mean (SD)	56.13 (40.72)	34.46 (17.92)
SE	6.14	6.77
Median	58.00	35.00
Min, Max	1.0, 145.6	10.0, 59.3
Change from baseline		
n	44	7
Mean (SD)	2.65 (13.12)	-5.02 (8.82)
SE	1.98	3.34
Median	1.50	-0.50
Min, Max	-26.5, 41.4	-17.5, 4.0

mNIS+7 score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurologic impairment (range = 0 to 304). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

Alnylam Pharmaceuticals Inc.
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Table 2.7
Modified Neuropathy Impairment Score +7 (mNIS+7): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Genotype: V30M

Subgroup Visit	Vutrisiran (HELIOS-A) (N=54)	Patisiran (HELIOS-A) (N=20)
Baseline		
n	54	20
Mean (SD)	64.00 (37.57)	63.18 (32.54)
SE	5.11	7.28
Median	70.88	57.94
Min, Max	3.0, 140.6	14.5, 137.6
Month 9		
Actual Value		
n	52	20
Mean (SD)	61.87 (37.75)	61.96 (31.74)
SE	5.23	7.10
Median	67.69	64.38
Min, Max	3.5, 137.5	11.5, 153.5
Change from baseline		
n	52	20
Mean (SD)	-1.10 (11.46)	-1.22 (14.96)
SE	1.59	3.35
Median	-0.44	-0.13
Min, Max	-29.5, 25.5	-47.0, 24.0

mNIS+7 score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurologic impairment (range = 0 to 304). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

Alnylam Pharmaceuticals Inc.
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Table 2.7
Modified Neuropathy Impairment Score +7 (mNIS+7): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Genotype: V30M

Subgroup Visit	Vutrisiran (HELIOS-A) (N=54)	Patisiran (HELIOS-A) (N=20)
Month 18		
Actual Value		
n	52	19
Mean (SD)	62.85 (38.90)	61.05 (29.26)
SE	5.39	6.71
Median	71.50	58.50
Min, Max	1.0, 145.6	16.0, 141.5
Change from baseline		
n	52	19
Mean (SD)	0.20 (13.21)	-1.17 (10.87)
SE	1.83	2.49
Median	0.38	1.50
Min, Max	-37.8, 41.4	-30.4, 15.0

mNIS+7 score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurologic impairment (range = 0 to 304). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

Alnylam Pharmaceuticals Inc.
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Table 2.7
Modified Neuropathy Impairment Score +7 (mNIS+7): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Genotype: non-V30M

Subgroup Visit	Vutrisiran (HELIOS-A) (N=68)	Patisiran (HELIOS-A) (N=22)
Baseline		
n	68	22
Mean (SD)	57.85 (34.73)	52.67 (34.72)
SE	4.21	7.40
Median	51.75	47.58
Min, Max	2.5, 158.0	7.0, 116.4
Month 9		
Actual Value		
n	65	20
Mean (SD)	55.25 (37.94)	47.42 (40.92)
SE	4.71	9.15
Median	45.00	39.25
Min, Max	1.0, 160.1	6.0, 152.3
Change from baseline		
n	65	20
Mean (SD)	-1.34 (14.61)	0.41 (19.57)
SE	1.81	4.38
Median	0.00	-3.50
Min, Max	-35.0, 26.0	-29.0, 62.9

mNIS+7 score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurologic impairment (range = 0 to 304). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Alnylam Pharmaceuticals Inc.
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Table 2.7
Modified Neuropathy Impairment Score +7 (mNIS+7): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Genotype: non-V30M

Subgroup Visit	Vutrisiran (HELIOS-A) (N=68)	Patisiran (HELIOS-A) (N=22)
Month 18		
Actual Value		
n	63	17
Mean (SD)	58.93 (41.66)	48.38 (46.35)
SE	5.25	11.24
Median	50.00	30.50
Min, Max	2.0, 164.8	8.5, 167.9
Change from baseline		
n	63	17
Mean (SD)	1.51 (16.29)	4.66 (29.32)
SE	2.05	7.11
Median	-1.00	0.50
Min, Max	-26.5, 59.0	-26.5, 106.1

mNIS+7 score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurologic impairment (range = 0 to 304). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

Alnylam Pharmaceuticals Inc.
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Table 2.7
Modified Neuropathy Impairment Score +7 (mNIS+7): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

FAP Stage: I

Subgroup Visit	Vutrisiran (HELIOS-A) (N=84)	Patisiran (HELIOS-A) (N=31)
Baseline		
n	84	31
Mean (SD)	49.72 (34.01)	45.98 (27.53)
SE	3.71	4.94
Median	40.00	41.50
Min, Max	2.5, 135.5	7.0, 115.9
Month 9		
Actual Value		
n	82	30
Mean (SD)	45.92 (34.68)	43.60 (29.79)
SE	3.83	5.44
Median	33.25	40.50
Min, Max	1.0, 137.5	6.0, 124.6
Change from baseline		
n	82	30
Mean (SD)	-2.68 (12.99)	-0.11 (16.18)
SE	1.43	2.95
Median	-0.75	-1.25
Min, Max	-35.0, 26.0	-29.0, 62.9

mNIS+7 score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurologic impairment (range = 0 to 304). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

Alnylam Pharmaceuticals Inc.
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Table 2.7
Modified Neuropathy Impairment Score +7 (mNIS+7): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

FAP Stage: I

Subgroup Visit	Vutrisiran (HELIOS-A) (N=84)	Patisiran (HELIOS-A) (N=31)
Month 18		
Actual Value		
n	81	29
Mean (SD)	47.93 (36.18)	44.62 (32.40)
SE	4.02	6.02
Median	33.00	35.00
Min, Max	1.0, 129.4	8.5, 167.9
Change from baseline		
n	81	29
Mean (SD)	-0.71 (14.63)	2.18 (23.36)
SE	1.63	4.34
Median	-1.00	1.50
Min, Max	-37.8, 59.0	-30.4, 106.1

mNIS+7 score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurologic impairment (range = 0 to 304). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

Alnylam Pharmaceuticals Inc.
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Table 2.7
Modified Neuropathy Impairment Score +7 (mNIS+7): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

FAP Stage: II&III

Subgroup Visit	Vutrisiran (HELIOS-A) (N=38)	Patisiran (HELIOS-A) (N=11)
Baseline		
n	38	11
Mean (SD)	84.56 (27.99)	90.64 (27.68)
SE	4.54	8.35
Median	83.94	90.13
Min, Max	30.0, 158.0	35.5, 137.6
Month 9		
Actual Value		
n	35	10
Mean (SD)	86.93 (28.38)	87.95 (37.39)
SE	4.80	11.82
Median	88.88	79.06
Min, Max	27.5, 160.1	35.9, 153.5
Change from baseline		
n	35	10
Mean (SD)	2.16 (13.42)	-1.29 (20.96)
SE	2.27	6.63
Median	2.25	-2.31
Min, Max	-27.4, 23.5	-47.0, 35.9

mNIS+7 score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurologic impairment (range = 0 to 304). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

Alnylam Pharmaceuticals Inc.
ALN-TTRSC02-002

Table 2.7
Modified Neuropathy Impairment Score +7 (mNIS+7): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

FAP Stage: II&III

Subgroup Visit	Vutrisiran (HELIOS-A) (N=38)	Patisiran (HELIOS-A) (N=11)
Month 18		
Actual Value		
n	34	7
Mean (SD)	91.13 (32.92)	98.35 (30.45)
SE	5.65	11.51
Median	89.75	88.63
Min, Max	30.5, 164.8	59.3, 141.5
Change from baseline		
n	34	7
Mean (SD)	4.80 (15.12)	-0.85 (11.98)
SE	2.59	4.53
Median	2.31	-1.75
Min, Max	-23.0, 50.6	-16.8, 21.0

mNIS+7 score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurologic impairment (range = 0 to 304). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Alnylam Pharmaceuticals Inc.
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Table 2.7
Modified Neuropathy Impairment Score +7 (mNIS+7): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Cardiac Subpopulation: Yes

Subgroup Visit	Vutrisiran (HELIOS-A) (N=40)	Patisiran (HELIOS-A) (N=14)
Baseline		
n	40	14
Mean (SD)	72.38 (32.51)	63.08 (35.72)
SE	5.14	9.55
Median	77.38	61.88
Min, Max	2.5, 158.0	13.0, 137.6
Month 9		
Actual Value		
n	38	14
Mean (SD)	73.69 (37.92)	71.57 (46.39)
SE	6.15	12.40
Median	78.50	68.25
Min, Max	1.0, 160.1	6.0, 153.5
Change from baseline		
n	38	14
Mean (SD)	1.56 (11.32)	8.49 (20.71)
SE	1.84	5.54
Median	-0.06	0.86
Min, Max	-28.0, 23.5	-10.5, 62.9

mNIS+7 score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurologic impairment (range = 0 to 304). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Alnylam Pharmaceuticals Inc.
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Table 2.7
Modified Neuropathy Impairment Score +7 (mNIS+7): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Cardiac Subpopulation: Yes

Subgroup Visit	Vutrisiran (HELIOS-A) (N=40)	Patisiran (HELIOS-A) (N=14)
Month 18		
Actual Value		
n	37	13
Mean (SD)	77.01 (40.21)	73.30 (48.26)
SE	6.61	13.38
Median	88.00	59.33
Min, Max	4.0, 164.8	13.0, 167.9
Change from baseline		
n	37	13
Mean (SD)	5.38 (16.73)	11.60 (31.27)
SE	2.75	8.67
Median	1.50	3.88
Min, Max	-22.5, 59.0	-26.5, 106.1

mNIS+7 score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurologic impairment (range = 0 to 304). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 2.7
Modified Neuropathy Impairment Score +7 (mNIS+7): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Cardiac Subpopulation: No

Subgroup Visit	Vutrisiran (HELIOS-A) (N=82)	Patisiran (HELIOS-A) (N=28)
Baseline		
n	82	28
Mean (SD)	54.81 (36.39)	54.97 (32.99)
SE	4.02	6.24
Median	47.50	51.83
Min, Max	3.0, 140.6	7.0, 115.9
Month 9		
Actual Value		
n	79	26
Mean (SD)	50.73 (35.69)	45.60 (27.53)
SE	4.02	5.40
Median	44.38	42.75
Min, Max	3.5, 137.5	7.0, 89.5
Change from baseline		
n	79	26
Mean (SD)	-2.58 (13.95)	-5.19 (13.08)
SE	1.57	2.56
Median	-0.50	-2.00
Min, Max	-35.0, 26.0	-47.0, 10.5

mNIS+7 score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurologic impairment (range = 0 to 304). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 2.7
Modified Neuropathy Impairment Score +7 (mNIS+7): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Cardiac Subpopulation: No

Subgroup Visit	Vutrisiran (HELIOS-A) (N=82)	Patisiran (HELIOS-A) (N=28)
Month 18		
Actual Value		
n	78	23
Mean (SD)	52.96 (38.22)	44.76 (27.40)
SE	4.33	5.71
Median	43.25	35.00
Min, Max	1.0, 144.8	8.5, 96.3
Change from baseline		
n	78	23
Mean (SD)	-1.20 (13.60)	-4.07 (10.47)
SE	1.54	2.18
Median	-1.00	-0.50
Min, Max	-37.8, 50.6	-30.4, 8.0

mNIS+7 score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurologic impairment (range = 0 to 304). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Alnylam Pharmaceuticals Inc.
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Table 2.7
Modified Neuropathy Impairment Score +7 (mNIS+7): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Weight (kg): <65

Subgroup Visit	Vutrisiran (HELIOS-A) (N=46)	Patisiran (HELIOS-A) (N=15)
Baseline		
n	46	15
Mean (SD)	73.89 (34.15)	56.10 (34.82)
SE	5.04	8.99
Median	79.38	54.38
Min, Max	2.5, 158.0	8.0, 137.6
Month 9		
Actual Value		
n	44	15
Mean (SD)	71.72 (37.16)	59.27 (41.66)
SE	5.60	10.76
Median	74.63	50.25
Min, Max	1.0, 160.1	7.5, 153.5
Change from baseline		
n	44	15
Mean (SD)	-2.02 (11.61)	3.17 (17.70)
SE	1.75	4.57
Median	-1.50	-2.00
Min, Max	-28.0, 25.5	-7.8, 62.9

mNIS+7 score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurologic impairment (range = 0 to 304). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

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Table 2.7
Modified Neuropathy Impairment Score +7 (mNIS+7): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Weight (kg): <65

Subgroup Visit	Vutrisiran (HELIOS-A) (N=46)	Patisiran (HELIOS-A) (N=15)
Month 18		
Actual Value		
n	42	13
Mean (SD)	74.49 (39.22)	56.89 (49.94)
SE	6.05	13.85
Median	78.06	35.00
Min, Max	4.0, 164.8	10.0, 167.9
Change from baseline		
n	42	13
Mean (SD)	2.62 (13.33)	4.62 (31.92)
SE	2.06	8.85
Median	1.50	-0.50
Min, Max	-22.5, 50.6	-26.5, 106.1

mNIS+7 score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurologic impairment (range = 0 to 304). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Alnylam Pharmaceuticals Inc.
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Table 2.7
Modified Neuropathy Impairment Score +7 (mNIS+7): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Weight (kg): ≥65

Subgroup Visit	Vutrisiran (HELIOS-A) (N=76)	Patisiran (HELIOS-A) (N=27)
Baseline		
n	76	27
Mean (SD)	52.51 (34.87)	58.55 (33.72)
SE	4.00	6.49
Median	42.50	52.50
Min, Max	3.0, 140.6	7.0, 116.4
Month 9		
Actual Value		
n	73	25
Mean (SD)	50.03 (36.09)	51.95 (34.32)
SE	4.22	6.86
Median	35.00	52.00
Min, Max	3.5, 137.5	6.0, 152.3
Change from baseline		
n	73	25
Mean (SD)	-0.76 (14.20)	-2.55 (16.91)
SE	1.66	3.38
Median	0.50	-0.25
Min, Max	-35.0, 26.0	-47.0, 35.9

mNIS+7 score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurologic impairment (range = 0 to 304). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 2.7
Modified Neuropathy Impairment Score +7 (mNIS+7): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Weight (kg): ≥65

Subgroup Visit	Vutrisiran (HELIOS-A) (N=76)	Patisiran (HELIOS-A) (N=27)
Month 18		
Actual Value		
n	73	23
Mean (SD)	52.77 (39.01)	54.04 (31.07)
SE	4.57	6.48
Median	41.50	58.50
Min, Max	1.0, 145.6	8.5, 137.4
Change from baseline		
n	73	23
Mean (SD)	-0.06 (15.78)	-0.13 (13.09)
SE	1.85	2.73
Median	-1.00	1.50
Min, Max	-37.8, 59.0	-30.4, 25.0

mNIS+7 score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurologic impairment (range = 0 to 304). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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mNIS+7-Gesamtwert (Binäre Analyse)

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Table 2.4
Modified Neuropathy Impairment Score +7 (mNIS+7)
Binary Subgroup Analysis
mITT Population

Month 9

Analysis Visit Statistics	Vutrisiran (HELIOS-A) (N=122)	Patisiran (HELIOS-A) (N=42)
Age (years)		
<65		
Patients included in analysis, N1	76	31
<0 point increase from baseline, n(%)	38 (50.0)	18 (58.1)
≥0 point increase from baseline, n(%)	36 (47.4)	12 (38.7)
Missing, n(%)	2 (2.6)	1 (3.2)
<0 point increase from baseline, (95% CI)	50.0 (38.8, 61.2)	58.1 (40.7, 75.4)
Percentage difference (Vutrisiran − Patisiran), (95% CI)	-8.065 (-28.755, 12.626)	
Odds ratio (Vutrisiran/Patisiran), (95% CI) [1]	0.722 (0.311, 1.678)	
Relative risk (Vutrisiran/Patisiran), (95% CI) [1]	0.861 (0.592, 1.252)	
P-value [2]	0.4335	

N1 = Patients with missing postbaseline values due to COVID-19 or after initiation of local standard treatment for hATTR amyloidosis were included in analysis.
[1] Based on unstratified analysis.
In estimation of the odds ratio and relative risk, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the percentage difference or p-value.
[2] p-value based on the Wald test testing whether the relative risk equals to 1.
[3] p-value from a logistic regression using the penalized likelihood estimation (the FIRTH option) and with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Table 2.4
Modified Neuropathy Impairment Score +7 (mNIS+7)
Binary Subgroup Analysis
mITT Population

Month 9

Analysis Visit Statistics	Vutrisiran (HELIOS-A) (N=122)	Patisiran (HELIOS-A) (N=42)
≥65		
Patients included in analysis, N1	46	11
<0 point increase from baseline, n(%)	22 (47.8)	4 (36.4)
≥0 point increase from baseline, n(%)	21 (45.7)	6 (54.5)
Missing, n(%)	3 (6.5)	1 (9.1)
<0 point increase from baseline, (95% CI)	47.8 (33.4, 62.3)	36.4 (7.9, 64.8)
Percentage difference (Vutrisiran – Patisiran), (95% CI)	11.462 (-20.420, 43.345)	
Odds ratio (Vutrisiran/Patisiran), (95% CI) [1]	1.604 (0.413, 6.237)	
Relative risk (Vutrisiran/Patisiran), (95% CI) [1]	1.315 (0.569, 3.040)	
P-value [2]	0.5216	
p-value of Treatment*Age [3]	0.3616	

N1 = Patients with missing postbaseline values due to COVID-19 or after initiation of local standard treatment for hATTR amyloidosis were included in analysis.
[1] Based on unstratified analysis.
In estimation of the odds ratio and relative risk, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the percentage difference or p-value.
[2] p-value based on the Wald test testing whether the relative risk equals to 1.
[3] p-value from a logistic regression using the penalized likelihood estimation (the FIRTH option) and with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Table 2.4
Modified Neuropathy Impairment Score +7 (mNIS+7)
Binary Subgroup Analysis
mITT Population

Month 18

Analysis Visit Statistics	Vutrisiran (HELIOS-A) (N=122)	Patisiran (HELIOS-A) (N=42)
Age (years)		
<65		
Patients included in analysis, N1	76	31
<0 point increase from baseline, n(%)	41 (53.9)	11 (35.5)
≥0 point increase from baseline, n(%)	33 (43.4)	16 (51.6)
Missing, n(%)	2 (2.6)	4 (12.9)
<0 point increase from baseline, (95% CI)	53.9 (42.7, 65.2)	35.5 (18.6, 52.3)
Percentage difference (Vutrisiran – Patisiran), (95% CI)	18.463 (-1.767, 38.694)	
Odds ratio (Vutrisiran/Patisiran), (95% CI) [1]	2.130 (0.899, 5.048)	
Relative risk (Vutrisiran/Patisiran), (95% CI) [1]	1.520 (0.906, 2.552)	
P-value [2]	0.1130	

N1 = Patients with missing postbaseline values due to COVID-19 or after initiation of local standard treatment for hATTR amyloidosis were included in analysis.
[1] Based on unstratified analysis.
In estimation of the odds ratio and relative risk, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the percentage difference or p-value.
[2] p-value based on the Wald test testing whether the relative risk equals to 1.
[3] p-value from a logistic regression using the penalized likelihood estimation (the FIRTH option) and with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Table 2.4
Modified Neuropathy Impairment Score +7 (mNIS+7)
Binary Subgroup Analysis
mITT Population

Month 18

Analysis Visit Statistics	Vutrisiran (HELIOS-A) (N=122)	Patisiran (HELIOS-A) (N=42)
≥65		
Patients included in analysis, N1	46	11
<0 point increase from baseline, n(%)	17 (37.0)	5 (45.5)
≥0 point increase from baseline, n(%)	24 (52.2)	4 (36.4)
Missing, n(%)	5 (10.9)	2 (18.2)
<0 point increase from baseline, (95% CI)	37.0 (23.0, 50.9)	45.5 (16.0, 74.9)
Percentage difference (Vutrisiran – Patisiran), (95% CI)	-8.498 (-41.062, 24.066)	
Odds ratio (Vutrisiran/Patisiran), (95% CI) [1]	0.703 (0.186, 2.658)	
Relative risk (Vutrisiran/Patisiran), (95% CI) [1]	0.813 (0.384, 1.720)	
P-value [2]	0.5883	
p-value of Treatment*Age [3]	0.1775	

N1 = Patients with missing postbaseline values due to COVID-19 or after initiation of local standard treatment for hATTR amyloidosis were included in analysis.
[1] Based on unstratified analysis.
In estimation of the odds ratio and relative risk, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the percentage difference or p-value.
[2] p-value based on the Wald test testing whether the relative risk equals to 1.
[3] p-value from a logistic regression using the penalized likelihood estimation (the FIRTH option) and with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Table 2.4
Modified Neuropathy Impairment Score +7 (mNIS+7)
Binary Subgroup Analysis
mITT Population

Month 9

Analysis Visit Statistics	Vutrisiran (HELIOS-A) (N=122)	Patisiran (HELIOS-A) (N=42)
Sex		
Male		
Patients included in analysis, N1	79	27
<0 point increase from baseline, n(%)	32 (40.5)	13 (48.1)
≥0 point increase from baseline, n(%)	44 (55.7)	12 (44.4)
Missing, n(%)	3 (3.8)	2 (7.4)
<0 point increase from baseline, (95% CI)	40.5 (29.7, 51.3)	48.1 (29.3, 67.0)
Percentage difference (Vutrisiran – Patisiran), (95% CI)	-7.642 (-29.376, 14.093)	
Odds ratio (Vutrisiran/Patisiran), (95% CI) [1]	0.733 (0.305, 1.765)	
Relative risk (Vutrisiran/Patisiran), (95% CI) [1]	0.841 (0.524, 1.351)	
P-value [2]	0.4748	

N1 = Patients with missing postbaseline values due to COVID-19 or after initiation of local standard treatment for hATTR amyloidosis were included in analysis.
[1] Based on unstratified analysis.
In estimation of the odds ratio and relative risk, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the percentage difference or p-value.
[2] p-value based on the Wald test testing whether the relative risk equals to 1.
[3] p-value from a logistic regression using the penalized likelihood estimation (the FIRTH option) and with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Table 2.4
Modified Neuropathy Impairment Score +7 (mNIS+7)
Binary Subgroup Analysis
mITT Population

Month 9

Analysis Visit Statistics	Vutrisiran (HELIOS-A) (N=122)	Patisiran (HELIOS-A) (N=42)
Female		
Patients included in analysis, N1	43	15
<0 point increase from baseline, n(%)	28 (65.1)	9 (60.0)
≥0 point increase from baseline, n(%)	13 (30.2)	6 (40.0)
Missing, n(%)	2 (4.7)	0
<0 point increase from baseline, (95% CI)	65.1 (50.9, 79.4)	60.0 (35.2, 84.8)
Percentage difference (Vutrisiran – Patisiran), (95% CI)	5.116 (-23.477, 33.709)	
Odds ratio (Vutrisiran/Patisiran), (95% CI) [1]	1.244 (0.372, 4.167)	
Relative risk (Vutrisiran/Patisiran), (95% CI) [1]	1.085 (0.680, 1.732)	
P-value [2]	0.7316	
p-value of Treatment*Sex [3]	0.4800	

N1 = Patients with missing postbaseline values due to COVID-19 or after initiation of local standard treatment for hATTR amyloidosis were included in analysis.
[1] Based on unstratified analysis.
In estimation of the odds ratio and relative risk, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the percentage difference or p-value.
[2] p-value based on the Wald test testing whether the relative risk equals to 1.
[3] p-value from a logistic regression using the penalized likelihood estimation (the FIRTH option) and with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Table 2.4
Modified Neuropathy Impairment Score +7 (mNIS+7)
Binary Subgroup Analysis
mITT Population

Month 18

Analysis Visit Statistics	Vutrisiran (HELIOS-A) (N=122)	Patisiran (HELIOS-A) (N=42)
Sex		
Male		
Patients included in analysis, N1	79	27
<0 point increase from baseline, n(%)	37 (46.8)	7 (25.9)
≥0 point increase from baseline, n(%)	37 (46.8)	15 (55.6)
Missing, n(%)	5 (6.3)	5 (18.5)
<0 point increase from baseline, (95% CI)	46.8 (35.8, 57.8)	25.9 (9.4, 42.5)
Percentage difference (Vutrisiran – Patisiran), (95% CI)	20.910 (1.052, 40.767)	
Odds ratio (Vutrisiran/Patisiran), (95% CI) [1]	2.517 (0.957, 6.623)	
Relative risk (Vutrisiran/Patisiran), (95% CI) [1]	1.807 (0.916, 3.564)	
P-value [2]	0.0880	

N1 = Patients with missing postbaseline values due to COVID-19 or after initiation of local standard treatment for hATTR amyloidosis were included in analysis.
[1] Based on unstratified analysis.
In estimation of the odds ratio and relative risk, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the percentage difference or p-value.
[2] p-value based on the Wald test testing whether the relative risk equals to 1.
[3] p-value from a logistic regression using the penalized likelihood estimation (the FIRTH option) and with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Table 2.4
Modified Neuropathy Impairment Score +7 (mNIS+7)
Binary Subgroup Analysis
mITT Population

Month 18

Analysis Visit Statistics	Vutrisiran (HELIOS-A) (N=122)	Patisiran (HELIOS-A) (N=42)
Female		
Patients included in analysis, N1	43	15
<0 point increase from baseline, n(%)	21 (48.8)	9 (60.0)
≥0 point increase from baseline, n(%)	20 (46.5)	5 (33.3)
Missing, n(%)	2 (4.7)	1 (6.7)
<0 point increase from baseline, (95% CI)	48.8 (33.9, 63.8)	60.0 (35.2, 84.8)
Percentage difference (Vutrisiran – Patisiran), (95% CI)	-11.163 (-40.108, 17.783)	
Odds ratio (Vutrisiran/Patisiran), (95% CI) [1]	0.636 (0.193, 2.099)	
Relative risk (Vutrisiran/Patisiran), (95% CI) [1]	0.814 (0.487, 1.361)	
P-value [2]	0.4326	
p-value of Treatment*Sex [3]	0.0944	

N1 = Patients with missing postbaseline values due to COVID-19 or after initiation of local standard treatment for hATTR amyloidosis were included in analysis.
[1] Based on unstratified analysis.
In estimation of the odds ratio and relative risk, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the percentage difference or p-value.
[2] p-value based on the Wald test testing whether the relative risk equals to 1.
[3] p-value from a logistic regression using the penalized likelihood estimation (the FIRTH option) and with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Table 2.4
Modified Neuropathy Impairment Score +7 (mNIS+7)
Binary Subgroup Analysis
mITT Population

Month 9

Analysis Visit Statistics	Vutrisiran (HELIOS-A) (N=122)	Patisiran (HELIOS-A) (N=42)
Race		
White		
Patients included in analysis, N1	86	29
<0 point increase from baseline, n(%)	43 (50.0)	13 (44.8)
≥0 point increase from baseline, n(%)	40 (46.5)	15 (51.7)
Missing, n(%)	3 (3.5)	1 (3.4)
<0 point increase from baseline, (95% CI)	50.0 (39.4, 60.6)	44.8 (26.7, 62.9)
Percentage difference (Vutrisiran – Patisiran), (95% CI)	5.172 (-15.787, 26.132)	
Odds ratio (Vutrisiran/Patisiran), (95% CI) [1]	1.231 (0.529, 2.866)	
Relative risk (Vutrisiran/Patisiran), (95% CI) [1]	1.115 (0.707, 1.759)	
P-value [2]	0.6386	

N1 = Patients with missing postbaseline values due to COVID-19 or after initiation of local standard treatment for hATTR amyloidosis were included in analysis.
[1] Based on unstratified analysis.
In estimation of the odds ratio and relative risk, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the percentage difference or p-value.
[2] p-value based on the Wald test testing whether the relative risk equals to 1.
[3] p-value from a logistic regression using the penalized likelihood estimation (the FIRTH option) and with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Table 2.4
Modified Neuropathy Impairment Score +7 (mNIS+7)
Binary Subgroup Analysis
mITT Population

Month 9

Analysis Visit Statistics	Vutrisiran (HELIOS-A) (N=122)	Patisiran (HELIOS-A) (N=42)
All Other Races		
Patients included in analysis, N1	36	13
<0 point increase from baseline, n(%)	17 (47.2)	9 (69.2)
≥0 point increase from baseline, n(%)	17 (47.2)	3 (23.1)
Missing, n(%)	2 (5.6)	1 (7.7)
<0 point increase from baseline, (95% CI)	47.2 (30.9, 63.5)	69.2 (44.1, 94.3)
Percentage difference (Vutrisiran – Patisiran), (95% CI)	-22.009 (-51.932, 7.915)	
Odds ratio (Vutrisiran/Patisiran), (95% CI) [1]	0.398 (0.103, 1.530)	
Relative risk (Vutrisiran/Patisiran), (95% CI) [1]	0.682 (0.413, 1.125)	
P-value [2]	0.1342	
p-value of Treatment*Race [3]	0.1901	

N1 = Patients with missing postbaseline values due to COVID-19 or after initiation of local standard treatment for hATTR amyloidosis were included in analysis.
[1] Based on unstratified analysis.
In estimation of the odds ratio and relative risk, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the percentage difference or p-value.
[2] p-value based on the Wald test testing whether the relative risk equals to 1.
[3] p-value from a logistic regression using the penalized likelihood estimation (the FIRTH option) and with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Table 2.4
Modified Neuropathy Impairment Score +7 (mNIS+7)
Binary Subgroup Analysis
mITT Population

Month 18

Analysis Visit Statistics	Vutrisiran (HELIOS-A) (N=122)	Patisiran (HELIOS-A) (N=42)
Race		
White		
Patients included in analysis, N1	86	29
<0 point increase from baseline, n(%)	45 (52.3)	12 (41.4)
≥0 point increase from baseline, n(%)	37 (43.0)	13 (44.8)
Missing, n(%)	4 (4.7)	4 (13.8)
<0 point increase from baseline, (95% CI)	52.3 (41.8, 62.9)	41.4 (23.5, 59.3)
Percentage difference (Vutrisiran – Patisiran), (95% CI)	10.946 (-9.856, 31.749)	
Odds ratio (Vutrisiran/Patisiran), (95% CI) [1]	1.555 (0.664, 3.644)	
Relative risk (Vutrisiran/Patisiran), (95% CI) [1]	1.265 (0.784, 2.039)	
P-value [2]	0.3357	

N1 = Patients with missing postbaseline values due to COVID-19 or after initiation of local standard treatment for hATTR amyloidosis were included in analysis.
[1] Based on unstratified analysis.
In estimation of the odds ratio and relative risk, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the percentage difference or p-value.
[2] p-value based on the Wald test testing whether the relative risk equals to 1.
[3] p-value from a logistic regression using the penalized likelihood estimation (the FIRTH option) and with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Table 2.4
Modified Neuropathy Impairment Score +7 (mNIS+7)
Binary Subgroup Analysis
mITT Population

Month 18

Analysis Visit Statistics	Vutrisiran (HELIOS-A) (N=122)	Patisiran (HELIOS-A) (N=42)
All Other Races		
Patients included in analysis, N1	36	13
<0 point increase from baseline, n(%)	13 (36.1)	4 (30.8)
≥0 point increase from baseline, n(%)	20 (55.6)	7 (53.8)
Missing, n(%)	3 (8.3)	2 (15.4)
<0 point increase from baseline, (95% CI)	36.1 (20.4, 51.8)	30.8 (5.7, 55.9)
Percentage difference (Vutrisiran – Patisiran), (95% CI)	5.342 (-24.249, 34.933)	
Odds ratio (Vutrisiran/Patisiran), (95% CI) [1]	1.272 (0.326, 4.955)	
Relative risk (Vutrisiran/Patisiran), (95% CI) [1]	1.174 (0.466, 2.957)	
P-value [2]	0.7342	
p-value of Treatment*Race [3]	0.7721	

N1 = Patients with missing postbaseline values due to COVID-19 or after initiation of local standard treatment for hATTR amyloidosis were included in analysis.
[1] Based on unstratified analysis.
In estimation of the odds ratio and relative risk, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the percentage difference or p-value.
[2] p-value based on the Wald test testing whether the relative risk equals to 1.
[3] p-value from a logistic regression using the penalized likelihood estimation (the FIRTH option) and with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Table 2.4
Modified Neuropathy Impairment Score +7 (mNIS+7)
Binary Subgroup Analysis
mITT Population

Month 9

Analysis Visit Statistics	Vutrisiran (HELIOS-A) (N=122)	Patisiran (HELIOS-A) (N=42)
Region		
North America		
Patients included in analysis, N1	27	8
<0 point increase from baseline, n(%)	16 (59.3)	4 (50.0)
≥0 point increase from baseline, n(%)	9 (33.3)	4 (50.0)
Missing, n(%)	2 (7.4)	0
<0 point increase from baseline, (95% CI)	59.3 (40.7, 77.8)	50.0 (15.4, 84.6)
Percentage difference (Vutrisiran – Patisiran), (95% CI)	9.259 (-30.034, 48.552)	
Odds ratio (Vutrisiran/Patisiran), (95% CI) [1]	1.455 (0.298, 7.092)	
Relative risk (Vutrisiran/Patisiran), (95% CI) [1]	1.185 (0.554, 2.535)	
P-value [2]	0.6614	

N1 = Patients with missing postbaseline values due to COVID-19 or after initiation of local standard treatment for hATTR amyloidosis were included in analysis.
[1] Based on unstratified analysis.
In estimation of the odds ratio and relative risk, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the percentage difference or p-value.
[2] p-value based on the Wald test testing whether the relative risk equals to 1.
[3] p-value from a logistic regression using the penalized likelihood estimation (the FIRTH option) and with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Table 2.4
Modified Neuropathy Impairment Score +7 (mNIS+7)
Binary Subgroup Analysis
mITT Population

Month 9

Analysis Visit Statistics	Vutrisiran (HELIOS-A) (N=122)	Patisiran (HELIOS-A) (N=42)
Western Europe		
Patients included in analysis, N1	42	20
<0 point increase from baseline, n(%)	20 (47.6)	7 (35.0)
≥0 point increase from baseline, n(%)	20 (47.6)	11 (55.0)
Missing, n(%)	2 (4.8)	2 (10.0)
<0 point increase from baseline, (95% CI)	47.6 (32.5, 62.7)	35.0 (14.1, 55.9)
Percentage difference (Vutrisiran – Patisiran), (95% CI)	12.619 (-13.171, 38.409)	
Odds ratio (Vutrisiran/Patisiran), (95% CI) [1]	1.688 (0.562, 5.074)	
Relative risk (Vutrisiran/Patisiran), (95% CI) [1]	1.361 (0.692, 2.676)	
P-value [2]	0.3722	

N1 = Patients with missing postbaseline values due to COVID-19 or after initiation of local standard treatment for hATTR amyloidosis were included in analysis.
[1] Based on unstratified analysis.
In estimation of the odds ratio and relative risk, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the percentage difference or p-value.
[2] p-value based on the Wald test testing whether the relative risk equals to 1.
[3] p-value from a logistic regression using the penalized likelihood estimation (the FIRTH option) and with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Table 2.4
Modified Neuropathy Impairment Score +7 (mNIS+7)
Binary Subgroup Analysis
mITT Population

Month 9

Analysis Visit Statistics	Vutrisiran (HELIOS-A) (N=122)	Patisiran (HELIOS-A) (N=42)
Rest of World		
Patients included in analysis, N1	53	14
<0 point increase from baseline, n(%)	24 (45.3)	11 (78.6)
≥0 point increase from baseline, n(%)	28 (52.8)	3 (21.4)
Missing, n(%)	1 (1.9)	0
<0 point increase from baseline, (95% CI)	45.3 (31.9, 58.7)	78.6 (57.1, 100.0)
Percentage difference (Vutrisiran - Patisiran), (95% CI)	-33.288 (-58.618, -7.959)	
Odds ratio (Vutrisiran/Patisiran), (95% CI) [1]	0.226 (0.056, 0.903)	
Relative risk (Vutrisiran/Patisiran), (95% CI) [1]	0.576 (0.385, 0.862)	
P-value [2]	0.0074	
p-value of Treatment*Region [3]	0.0874	

N1 = Patients with missing postbaseline values due to COVID-19 or after initiation of local standard treatment for hATTR amyloidosis were included in analysis.
[1] Based on unstratified analysis.
In estimation of the odds ratio and relative risk, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the percentage difference or p-value.
[2] p-value based on the Wald test testing whether the relative risk equals to 1.
[3] p-value from a logistic regression using the penalized likelihood estimation (the FIRTH option) and with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Table 2.4
Modified Neuropathy Impairment Score +7 (mNIS+7)
Binary Subgroup Analysis
mITT Population

Month 18

Analysis Visit Statistics	Vutrisiran (HELIOS-A) (N=122)	Patisiran (HELIOS-A) (N=42)
Region		
North America		
Patients included in analysis, N1	27	8
<0 point increase from baseline, n(%)	18 (66.7)	4 (50.0)
≥0 point increase from baseline, n(%)	7 (25.9)	2 (25.0)
Missing, n(%)	2 (7.4)	2 (25.0)
<0 point increase from baseline, (95% CI)	66.7 (48.9, 84.4)	50.0 (15.4, 84.6)
Percentage difference (Vutrisiran – Patisiran), (95% CI)	16.667 (-22.277, 55.611)	
Odds ratio (Vutrisiran/Patisiran), (95% CI) [1]	2.000 (0.404, 9.909)	
Relative risk (Vutrisiran/Patisiran), (95% CI) [1]	1.333 (0.635, 2.802)	
P-value [2]	0.4476	

N1 = Patients with missing postbaseline values due to COVID-19 or after initiation of local standard treatment for hATTR amyloidosis were included in analysis.
[1] Based on unstratified analysis.
In estimation of the odds ratio and relative risk, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the percentage difference or p-value.
[2] p-value based on the Wald test testing whether the relative risk equals to 1.
[3] p-value from a logistic regression using the penalized likelihood estimation (the FIRTH option) and with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Table 2.4
Modified Neuropathy Impairment Score +7 (mNIS+7)
Binary Subgroup Analysis
mITT Population

Month 18

Analysis Visit Statistics	Vutrisiran (HELIOS-A) (N=122)	Patisiran (HELIOS-A) (N=42)
Western Europe		
Patients included in analysis, N1	42	20
<0 point increase from baseline, n(%)	20 (47.6)	8 (40.0)
≥0 point increase from baseline, n(%)	20 (47.6)	9 (45.0)
Missing, n(%)	2 (4.8)	3 (15.0)
<0 point increase from baseline, (95% CI)	47.6 (32.5, 62.7)	40.0 (18.5, 61.5)
Percentage difference (Vutrisiran – Patisiran), (95% CI)	7.619 (-18.632, 33.870)	
Odds ratio (Vutrisiran/Patisiran), (95% CI) [1]	1.364 (0.463, 4.017)	
Relative risk (Vutrisiran/Patisiran), (95% CI) [1]	1.190 (0.638, 2.221)	
P-value [2]	0.5836	

N1 = Patients with missing postbaseline values due to COVID-19 or after initiation of local standard treatment for hATTR amyloidosis were included in analysis.
[1] Based on unstratified analysis.
In estimation of the odds ratio and relative risk, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the percentage difference or p-value.
[2] p-value based on the Wald test testing whether the relative risk equals to 1.
[3] p-value from a logistic regression using the penalized likelihood estimation (the FIRTH option) and with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Table 2.4
Modified Neuropathy Impairment Score +7 (mNIS+7)
Binary Subgroup Analysis
mITT Population

Month 18

Analysis Visit Statistics	Vutrisiran (HELIOS-A) (N=122)	Patisiran (HELIOS-A) (N=42)
Rest of World		
Patients included in analysis, N1	53	14
<0 point increase from baseline, n(%)	20 (37.7)	4 (28.6)
≥0 point increase from baseline, n(%)	30 (56.6)	9 (64.3)
Missing, n(%)	3 (5.7)	1 (7.1)
<0 point increase from baseline, (95% CI)	37.7 (24.7, 50.8)	28.6 (4.9, 52.2)
Percentage difference (Vutrisiran – Patisiran), (95% CI)	9.164 (-17.859, 36.188)	
Odds ratio (Vutrisiran/Patisiran), (95% CI) [1]	1.515 (0.419, 5.481)	
Relative risk (Vutrisiran/Patisiran), (95% CI) [1]	1.321 (0.538, 3.241)	
P-value [2]	0.5435	
p-value of Treatment*Region [3]	0.9284	

N1 = Patients with missing postbaseline values due to COVID-19 or after initiation of local standard treatment for hATTR amyloidosis were included in analysis.
[1] Based on unstratified analysis.
In estimation of the odds ratio and relative risk, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the percentage difference or p-value.
[2] p-value based on the Wald test testing whether the relative risk equals to 1.
[3] p-value from a logistic regression using the penalized likelihood estimation (the FIRTH option) and with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Table 2.4
Modified Neuropathy Impairment Score +7 (mNIS+7)
Binary Subgroup Analysis
mITT Population

Month 9

Analysis Visit Statistics	Vutrisiran (HELIOS-A) (N=122)	Patisiran (HELIOS-A) (N=42)
Baseline NIS		
<50		
Patients included in analysis, N1	78	27
<0 point increase from baseline, n(%)	41 (52.6)	15 (55.6)
≥0 point increase from baseline, n(%)	36 (46.2)	12 (44.4)
Missing, n(%)	1 (1.3)	0
<0 point increase from baseline, (95% CI)	52.6 (41.5, 63.6)	55.6 (36.8, 74.3)
Percentage difference (Vutrisiran – Patisiran), (95% CI)	-2.991 (-24.765, 18.782)	
Odds ratio (Vutrisiran/Patisiran), (95% CI) [1]	0.886 (0.368, 2.136)	
Relative risk (Vutrisiran/Patisiran), (95% CI) [1]	0.946 (0.636, 1.408)	
P-value [2]	0.7851	

N1 = Patients with missing postbaseline values due to COVID-19 or after initiation of local standard treatment for hATTR amyloidosis were included in analysis.
[1] Based on unstratified analysis.
In estimation of the odds ratio and relative risk, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the percentage difference or p-value.
[2] p-value based on the Wald test testing whether the relative risk equals to 1.
[3] p-value from a logistic regression using the penalized likelihood estimation (the FIRTH option) and with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Table 2.4
Modified Neuropathy Impairment Score +7 (mNIS+7)
Binary Subgroup Analysis
mITT Population

Month 9

Analysis Visit Statistics	Vutrisiran (HELIOS-A) (N=122)	Patisiran (HELIOS-A) (N=42)
≥50		
Patients included in analysis, N1	44	15
<0 point increase from baseline, n(%)	19 (43.2)	7 (46.7)
≥0 point increase from baseline, n(%)	21 (47.7)	6 (40.0)
Missing, n(%)	4 (9.1)	2 (13.3)
<0 point increase from baseline, (95% CI)	43.2 (28.5, 57.8)	46.7 (21.4, 71.9)
Percentage difference (Vutrisiran – Patisiran), (95% CI)	-3.485 (-32.667, 25.697)	
Odds ratio (Vutrisiran/Patisiran), (95% CI) [1]	0.869 (0.268, 2.818)	
Relative risk (Vutrisiran/Patisiran), (95% CI) [1]	0.925 (0.489, 1.752)	
P-value [2]	0.8117	
p-value of Treatment*Baseline NIS [3]	0.9688	

N1 = Patients with missing postbaseline values due to COVID-19 or after initiation of local standard treatment for hATTR amyloidosis were included in analysis.
[1] Based on unstratified analysis.
In estimation of the odds ratio and relative risk, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the percentage difference or p-value.
[2] p-value based on the Wald test testing whether the relative risk equals to 1.
[3] p-value from a logistic regression using the penalized likelihood estimation (the FIRTH option) and with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Table 2.4
Modified Neuropathy Impairment Score +7 (mNIS+7)
Binary Subgroup Analysis
mITT Population

Month 18

Analysis Visit Statistics	Vutrisiran (HELIOS-A) (N=122)	Patisiran (HELIOS-A) (N=42)
Baseline NIS		
<50		
Patients included in analysis, N1	78	27
<0 point increase from baseline, n(%)	42 (53.8)	10 (37.0)
≥0 point increase from baseline, n(%)	33 (42.3)	15 (55.6)
Missing, n(%)	3 (3.8)	2 (7.4)
<0 point increase from baseline, (95% CI)	53.8 (42.8, 64.9)	37.0 (18.8, 55.3)
Percentage difference (Vutrisiran – Patisiran), (95% CI)	16.809 (-4.502, 38.121)	
Odds ratio (Vutrisiran/Patisiran), (95% CI) [1]	1.983 (0.807, 4.874)	
Relative risk (Vutrisiran/Patisiran), (95% CI) [1]	1.454 (0.853, 2.477)	
P-value [2]	0.1688	

N1 = Patients with missing postbaseline values due to COVID-19 or after initiation of local standard treatment for hATTR amyloidosis were included in analysis.
[1] Based on unstratified analysis.
In estimation of the odds ratio and relative risk, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the percentage difference or p-value.
[2] p-value based on the Wald test testing whether the relative risk equals to 1.
[3] p-value from a logistic regression using the penalized likelihood estimation (the FIRTH option) and with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Table 2.4
Modified Neuropathy Impairment Score +7 (mNIS+7)
Binary Subgroup Analysis
mITT Population

Month 18

Analysis Visit Statistics	Vutrisiran (HELIOS-A) (N=122)	Patisiran (HELIOS-A) (N=42)
≥50		
Patients included in analysis, N1	44	15
<0 point increase from baseline, n(%)	16 (36.4)	6 (40.0)
≥0 point increase from baseline, n(%)	24 (54.5)	5 (33.3)
Missing, n(%)	4 (9.1)	4 (26.7)
<0 point increase from baseline, (95% CI)	36.4 (22.1, 50.6)	40.0 (15.2, 64.8)
Percentage difference (Vutrisiran - Patisiran), (95% CI)	-3.636 (-32.214, 24.941)	
Odds ratio (Vutrisiran/Patisiran), (95% CI) [1]	0.857 (0.258, 2.851)	
Relative risk (Vutrisiran/Patisiran), (95% CI) [1]	0.909 (0.437, 1.892)	
P-value [2]	0.7988	
p-value of Treatment*Baseline NIS [3]	0.2774	

N1 = Patients with missing postbaseline values due to COVID-19 or after initiation of local standard treatment for hATTR amyloidosis were included in analysis.
[1] Based on unstratified analysis.
In estimation of the odds ratio and relative risk, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the percentage difference or p-value.
[2] p-value based on the Wald test testing whether the relative risk equals to 1.
[3] p-value from a logistic regression using the penalized likelihood estimation (the FIRTH option) and with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Table 2.4
Modified Neuropathy Impairment Score +7 (mNIS+7)
Binary Subgroup Analysis
mITT Population

Month 9

Analysis Visit Statistics	Vutrisiran (HELIOS-A) (N=122)	Patisiran (HELIOS-A) (N=42)
Previous Tetramer Stabilizer Use		
Yes		
Patients included in analysis, N1	75	33
<0 point increase from baseline, n(%)	42 (56.0)	17 (51.5)
≥0 point increase from baseline, n(%)	32 (42.7)	15 (45.5)
Missing, n(%)	1 (1.3)	1 (3.0)
<0 point increase from baseline, (95% CI)	56.0 (44.8, 67.2)	51.5 (34.5, 68.6)
Percentage difference (Vutrisiran – Patisiran), (95% CI)	4.485 (-15.935, 24.904)	
Odds ratio (Vutrisiran/Patisiran), (95% CI) [1]	1.198 (0.527, 2.722)	
Relative risk (Vutrisiran/Patisiran), (95% CI) [1]	1.087 (0.738, 1.601)	
P-value [2]	0.6725	

N1 = Patients with missing postbaseline values due to COVID-19 or after initiation of local standard treatment for hATTR amyloidosis were included in analysis.
[1] Based on unstratified analysis.
In estimation of the odds ratio and relative risk, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the percentage difference or p-value.
[2] p-value based on the Wald test testing whether the relative risk equals to 1.
[3] p-value from a logistic regression using the penalized likelihood estimation (the FIRTH option) and with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Table 2.4
Modified Neuropathy Impairment Score +7 (mNIS+7)
Binary Subgroup Analysis
mITT Population

Month 9

Analysis Visit Statistics	Vutrisiran (HELIOS-A) (N=122)	Patisiran (HELIOS-A) (N=42)
No		
Patients included in analysis, N1	47	9
<0 point increase from baseline, n(%)	18 (38.3)	5 (55.6)
≥0 point increase from baseline, n(%)	25 (53.2)	3 (33.3)
Missing, n(%)	4 (8.5)	1 (11.1)
<0 point increase from baseline, (95% CI)	38.3 (24.4, 52.2)	55.6 (23.1, 88.0)
Percentage difference (Vutrisiran – Patisiran), (95% CI)	-17.258 (-52.571, 18.056)	
Odds ratio (Vutrisiran/Patisiran), (95% CI) [1]	0.497 (0.118, 2.096)	
Relative risk (Vutrisiran/Patisiran), (95% CI) [1]	0.689 (0.347, 1.371)	
P-value [2]	0.2892	
p-value of Treatment*Previous Tetramer Stabilizer Use [3]	0.3164	

N1 = Patients with missing postbaseline values due to COVID-19 or after initiation of local standard treatment for hATTR amyloidosis were included in analysis.
[1] Based on unstratified analysis.
In estimation of the odds ratio and relative risk, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the percentage difference or p-value.
[2] p-value based on the Wald test testing whether the relative risk equals to 1.
[3] p-value from a logistic regression using the penalized likelihood estimation (the FIRTH option) and with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Table 2.4
Modified Neuropathy Impairment Score +7 (mNIS+7)
Binary Subgroup Analysis
mITT Population

Month 18

Analysis Visit Statistics	Vutrisiran (HELIOS-A) (N=122)	Patisiran (HELIOS-A) (N=42)
Previous Tetramer Stabilizer Use		
Yes		
Patients included in analysis, N1	75	33
<0 point increase from baseline, n(%)	39 (52.0)	12 (36.4)
≥0 point increase from baseline, n(%)	32 (42.7)	17 (51.5)
Missing, n(%)	4 (5.3)	4 (12.1)
<0 point increase from baseline, (95% CI)	52.0 (40.7, 63.3)	36.4 (20.0, 52.8)
Percentage difference (Vutrisiran – Patisiran), (95% CI)	15.636 (-4.294, 35.567)	
Odds ratio (Vutrisiran/Patisiran), (95% CI) [1]	1.896 (0.817, 4.398)	
Relative risk (Vutrisiran/Patisiran), (95% CI) [1]	1.430 (0.866, 2.360)	
P-value [2]	0.1617	

N1 = Patients with missing postbaseline values due to COVID-19 or after initiation of local standard treatment for hATTR amyloidosis were included in analysis.
[1] Based on unstratified analysis.
In estimation of the odds ratio and relative risk, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the percentage difference or p-value.
[2] p-value based on the Wald test testing whether the relative risk equals to 1.
[3] p-value from a logistic regression using the penalized likelihood estimation (the FIRTH option) and with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Table 2.4
Modified Neuropathy Impairment Score +7 (mNIS+7)
Binary Subgroup Analysis
mITT Population

Month 18

Analysis Visit Statistics	Vutrisiran (HELIOS-A) (N=122)	Patisiran (HELIOS-A) (N=42)
No		
Patients included in analysis, N1	47	9
<0 point increase from baseline, n(%)	19 (40.4)	4 (44.4)
≥0 point increase from baseline, n(%)	25 (53.2)	3 (33.3)
Missing, n(%)	3 (6.4)	2 (22.2)
<0 point increase from baseline, (95% CI)	40.4 (26.4, 54.5)	44.4 (12.0, 76.9)
Percentage difference (Vutrisiran – Patisiran), (95% CI)	-4.019 (-39.385, 31.347)	
Odds ratio (Vutrisiran/Patisiran), (95% CI) [1]	0.848 (0.201, 3.573)	
Relative risk (Vutrisiran/Patisiran), (95% CI) [1]	0.910 (0.405, 2.042)	
P-value [2]	0.8183	
p-value of Treatment*Previous Tetramer Stabilizer Use [3]	0.3460	

N1 = Patients with missing postbaseline values due to COVID-19 or after initiation of local standard treatment for hATTR amyloidosis were included in analysis.
[1] Based on unstratified analysis.
In estimation of the odds ratio and relative risk, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the percentage difference or p-value.
[2] p-value based on the Wald test testing whether the relative risk equals to 1.
[3] p-value from a logistic regression using the penalized likelihood estimation (the FIRTH option) and with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Table 2.4
Modified Neuropathy Impairment Score +7 (mNIS+7)
Binary Subgroup Analysis
mITT Population

Month 9

Analysis Visit Statistics	Vutrisiran (HELIOS-A) (N=122)	Patisiran (HELIOS-A) (N=42)
Genotype		
V30M		
Patients included in analysis, N1	54	20
<0 point increase from baseline, n(%)	28 (51.9)	10 (50.0)
≥0 point increase from baseline, n(%)	24 (44.4)	10 (50.0)
Missing, n(%)	2 (3.7)	0
<0 point increase from baseline, (95% CI)	51.9 (38.5, 65.2)	50.0 (28.1, 71.9)
Percentage difference (Vutrisiran – Patisiran), (95% CI)	1.852 (-23.795, 27.499)	
Odds ratio (Vutrisiran/Patisiran), (95% CI) [1]	1.077 (0.386, 3.005)	
Relative risk (Vutrisiran/Patisiran), (95% CI) [1]	1.037 (0.624, 1.724)	
P-value [2]	0.8884	

N1 = Patients with missing postbaseline values due to COVID-19 or after initiation of local standard treatment for hATTR amyloidosis were included in analysis.
[1] Based on unstratified analysis.
In estimation of the odds ratio and relative risk, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the percentage difference or p-value.
[2] p-value based on the Wald test testing whether the relative risk equals to 1.
[3] p-value from a logistic regression using the penalized likelihood estimation (the FIRTH option) and with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Table 2.4
Modified Neuropathy Impairment Score +7 (mNIS+7)
Binary Subgroup Analysis
mITT Population

Month 9

Analysis Visit Statistics	Vutrisiran (HELIOS-A) (N=122)	Patisiran (HELIOS-A) (N=42)
non-V30M		
Patients included in analysis, N1	68	22
<0 point increase from baseline, n(%)	32 (47.1)	12 (54.5)
≥0 point increase from baseline, n(%)	33 (48.5)	8 (36.4)
Missing, n(%)	3 (4.4)	2 (9.1)
<0 point increase from baseline, (95% CI)	47.1 (35.2, 58.9)	54.5 (33.7, 75.4)
Percentage difference (Vutrisiran - Patisiran), (95% CI)	-7.487 (-31.438, 16.465)	
Odds ratio (Vutrisiran/Patisiran), (95% CI) [1]	0.741 (0.282, 1.944)	
Relative risk (Vutrisiran/Patisiran), (95% CI) [1]	0.863 (0.546, 1.363)	
P-value [2]	0.5268	
p-value of Treatment*Genotype [3]	0.6137	

N1 = Patients with missing postbaseline values due to COVID-19 or after initiation of local standard treatment for hATTR amyloidosis were included in analysis.
[1] Based on unstratified analysis.
In estimation of the odds ratio and relative risk, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the percentage difference or p-value.
[2] p-value based on the Wald test testing whether the relative risk equals to 1.
[3] p-value from a logistic regression using the penalized likelihood estimation (the FIRTH option) and with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Alnylam Pharmaceuticals Inc.
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Table 2.4
Modified Neuropathy Impairment Score +7 (mNIS+7)
Binary Subgroup Analysis
mITT Population

Month 18

Analysis Visit Statistics	Vutrisiran (HELIOS-A) (N=122)	Patisiran (HELIOS-A) (N=42)
Genotype		
V30M		
Patients included in analysis, N1	54	20
<0 point increase from baseline, n(%)	24 (44.4)	9 (45.0)
≥0 point increase from baseline, n(%)	28 (51.9)	10 (50.0)
Missing, n(%)	2 (3.7)	1 (5.0)
<0 point increase from baseline, (95% CI)	44.4 (31.2, 57.7)	45.0 (23.2, 66.8)
Percentage difference (Vutrisiran – Patisiran), (95% CI)	-0.556 (-26.071, 24.960)	
Odds ratio (Vutrisiran/Patisiran), (95% CI) [1]	0.978 (0.349, 2.743)	
Relative risk (Vutrisiran/Patisiran), (95% CI) [1]	0.988 (0.559, 1.745)	
P-value [2]	0.9659	

N1 = Patients with missing postbaseline values due to COVID-19 or after initiation of local standard treatment for hATTR amyloidosis were included in analysis.
[1] Based on unstratified analysis.
In estimation of the odds ratio and relative risk, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the percentage difference or p-value.
[2] p-value based on the Wald test testing whether the relative risk equals to 1.
[3] p-value from a logistic regression using the penalized likelihood estimation (the FIRTH option) and with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Table 2.4
Modified Neuropathy Impairment Score +7 (mNIS+7)
Binary Subgroup Analysis
mITT Population

Month 18

Analysis Visit Statistics	Vutrisiran (HELIOS-A) (N=122)	Patisiran (HELIOS-A) (N=42)
non-V30M		
Patients included in analysis, N1	68	22
<0 point increase from baseline, n(%)	34 (50.0)	7 (31.8)
≥0 point increase from baseline, n(%)	29 (42.6)	10 (45.5)
Missing, n(%)	5 (7.4)	5 (22.7)
<0 point increase from baseline, (95% CI)	50.0 (38.1, 61.9)	31.8 (12.4, 51.3)
Percentage difference (Vutrisiran - Patisiran), (95% CI)	18.182 (-4.622, 40.986)	
Odds ratio (Vutrisiran/Patisiran), (95% CI) [1]	2.143 (0.776, 5.915)	
Relative risk (Vutrisiran/Patisiran), (95% CI) [1]	1.571 (0.815, 3.029)	
P-value [2]	0.1770	
p-value of Treatment*Genotype [3]	0.3060	

N1 = Patients with missing postbaseline values due to COVID-19 or after initiation of local standard treatment for hATTR amyloidosis were included in analysis.
[1] Based on unstratified analysis.
In estimation of the odds ratio and relative risk, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the percentage difference or p-value.
[2] p-value based on the Wald test testing whether the relative risk equals to 1.
[3] p-value from a logistic regression using the penalized likelihood estimation (the FIRTH option) and with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Table 2.4
Modified Neuropathy Impairment Score +7 (mNIS+7)
Binary Subgroup Analysis
mITT Population

Month 9

Analysis Visit Statistics	Vutrisiran (HELIOS-A) (N=122)	Patisiran (HELIOS-A) (N=42)
FAP Stage		
I		
Patients included in analysis, N1	84	31
<0 point increase from baseline, n(%)	44 (52.4)	17 (54.8)
≥0 point increase from baseline, n(%)	38 (45.2)	13 (41.9)
Missing, n(%)	2 (2.4)	1 (3.2)
<0 point increase from baseline, (95% CI)	52.4 (41.7, 63.1)	54.8 (37.3, 72.4)
Percentage difference (Vutrisiran – Patisiran), (95% CI)	-2.458 (-22.975, 18.060)	
Odds ratio (Vutrisiran/Patisiran), (95% CI) [1]	0.906 (0.396, 2.071)	
Relative risk (Vutrisiran/Patisiran), (95% CI) [1]	0.955 (0.654, 1.395)	
P-value [2]	0.8125	

N1 = Patients with missing postbaseline values due to COVID-19 or after initiation of local standard treatment for hATTR amyloidosis were included in analysis.
[1] Based on unstratified analysis.
In estimation of the odds ratio and relative risk, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the percentage difference or p-value.
[2] p-value based on the Wald test testing whether the relative risk equals to 1.
[3] p-value from a logistic regression using the penalized likelihood estimation (the FIRTH option) and with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Table 2.4
Modified Neuropathy Impairment Score +7 (mNIS+7)
Binary Subgroup Analysis
mITT Population

Month 9

Analysis Visit Statistics	Vutrisiran (HELIOS-A) (N=122)	Patisiran (HELIOS-A) (N=42)
II&III		
Patients included in analysis, N1	38	11
<0 point increase from baseline, n(%)	16 (42.1)	5 (45.5)
≥0 point increase from baseline, n(%)	19 (50.0)	5 (45.5)
Missing, n(%)	3 (7.9)	1 (9.1)
<0 point increase from baseline, (95% CI)	42.1 (26.4, 57.8)	45.5 (16.0, 74.9)
Percentage difference (Vutrisiran – Patisiran), (95% CI)	-3.349 (-36.700, 30.001)	
Odds ratio (Vutrisiran/Patisiran), (95% CI) [1]	0.873 (0.226, 3.367)	
Relative risk (Vutrisiran/Patisiran), (95% CI) [1]	0.926 (0.439, 1.955)	
P-value [2]	0.8408	
p-value of Treatment*FAP Stage [3]	0.9515	

N1 = Patients with missing postbaseline values due to COVID-19 or after initiation of local standard treatment for hATTR amyloidosis were included in analysis.
[1] Based on unstratified analysis.
In estimation of the odds ratio and relative risk, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the percentage difference or p-value.
[2] p-value based on the Wald test testing whether the relative risk equals to 1.
[3] p-value from a logistic regression using the penalized likelihood estimation (the FIRTH option) and with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Table 2.4
Modified Neuropathy Impairment Score +7 (mNIS+7)
Binary Subgroup Analysis
mITT Population

Month 18

Analysis Visit Statistics	Vutrisiran (HELIOS-A) (N=122)	Patisiran (HELIOS-A) (N=42)
FAP Stage		
I		
Patients included in analysis, N1	84	31
<0 point increase from baseline, n(%)	44 (52.4)	12 (38.7)
≥0 point increase from baseline, n(%)	37 (44.0)	17 (54.8)
Missing, n(%)	3 (3.6)	2 (6.5)
<0 point increase from baseline, (95% CI)	52.4 (41.7, 63.1)	38.7 (21.6, 55.9)
Percentage difference (Vutrisiran – Patisiran), (95% CI)	13.671 (-6.529, 33.872)	
Odds ratio (Vutrisiran/Patisiran), (95% CI) [1]	1.742 (0.752, 4.034)	
Relative risk (Vutrisiran/Patisiran), (95% CI) [1]	1.353 (0.831, 2.204)	
P-value [2]	0.2241	

N1 = Patients with missing postbaseline values due to COVID-19 or after initiation of local standard treatment for hATTR amyloidosis were included in analysis.
[1] Based on unstratified analysis.
In estimation of the odds ratio and relative risk, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the percentage difference or p-value.
[2] p-value based on the Wald test testing whether the relative risk equals to 1.
[3] p-value from a logistic regression using the penalized likelihood estimation (the FIRTH option) and with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Table 2.4
Modified Neuropathy Impairment Score +7 (mNIS+7)
Binary Subgroup Analysis
mITT Population

Month 18

Analysis Visit Statistics	Vutrisiran (HELIOS-A) (N=122)	Patisiran (HELIOS-A) (N=42)
II&III		
Patients included in analysis, N1	38	11
<0 point increase from baseline, n(%)	14 (36.8)	4 (36.4)
≥0 point increase from baseline, n(%)	20 (52.6)	3 (27.3)
Missing, n(%)	4 (10.5)	4 (36.4)
<0 point increase from baseline, (95% CI)	36.8 (21.5, 52.2)	36.4 (7.9, 64.8)
Percentage difference (Vutrisiran – Patisiran), (95% CI)	0.478 (-31.822, 32.779)	
Odds ratio (Vutrisiran/Patisiran), (95% CI) [1]	1.021 (0.253, 4.115)	
Relative risk (Vutrisiran/Patisiran), (95% CI) [1]	1.013 (0.418, 2.457)	
P-value [2]	0.9769	
p-value of Treatment*FAP Stage [3]	0.5041	

N1 = Patients with missing postbaseline values due to COVID-19 or after initiation of local standard treatment for hATTR amyloidosis were included in analysis.
[1] Based on unstratified analysis.
In estimation of the odds ratio and relative risk, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the percentage difference or p-value.
[2] p-value based on the Wald test testing whether the relative risk equals to 1.
[3] p-value from a logistic regression using the penalized likelihood estimation (the FIRTH option) and with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Table 2.4
Modified Neuropathy Impairment Score +7 (mNIS+7)
Binary Subgroup Analysis
mITT Population

Month 9

Analysis Visit Statistics	Vutrisiran (HELIOS-A) (N=122)	Patisiran (HELIOS-A) (N=42)
Cardiac Subpopulation		
Yes		
Patients included in analysis, N1	40	14
<0 point increase from baseline, n(%)	19 (47.5)	6 (42.9)
≥0 point increase from baseline, n(%)	19 (47.5)	8 (57.1)
Missing, n(%)	2 (5.0)	0
<0 point increase from baseline, (95% CI)	47.5 (32.0, 63.0)	42.9 (16.9, 68.8)
Percentage difference (Vutrisiran – Patisiran), (95% CI)	4.643 (-25.548, 34.833)	
Odds ratio (Vutrisiran/Patisiran), (95% CI) [1]	1.206 (0.354, 4.115)	
Relative risk (Vutrisiran/Patisiran), (95% CI) [1]	1.108 (0.558, 2.203)	
P-value [2]	0.7692	

N1 = Patients with missing postbaseline values due to COVID-19 or after initiation of local standard treatment for hATTR amyloidosis were included in analysis.
[1] Based on unstratified analysis.
In estimation of the odds ratio and relative risk, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the percentage difference or p-value.
[2] p-value based on the Wald test testing whether the relative risk equals to 1.
[3] p-value from a logistic regression using the penalized likelihood estimation (the FIRTH option) and with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Table 2.4
Modified Neuropathy Impairment Score +7 (mNIS+7)
Binary Subgroup Analysis
mITT Population

Month 9

Analysis Visit Statistics	Vutrisiran (HELIOS-A) (N=122)	Patisiran (HELIOS-A) (N=42)
No		
Patients included in analysis, N1	82	28
<0 point increase from baseline, n(%)	41 (50.0)	16 (57.1)
≥0 point increase from baseline, n(%)	38 (46.3)	10 (35.7)
Missing, n(%)	3 (3.7)	2 (7.1)
<0 point increase from baseline, (95% CI)	50.0 (39.2, 60.8)	57.1 (38.8, 75.5)
Percentage difference (Vutrisiran – Patisiran), (95% CI)	-7.143 (-28.429, 14.143)	
Odds ratio (Vutrisiran/Patisiran), (95% CI) [1]	0.750 (0.316, 1.781)	
Relative risk (Vutrisiran/Patisiran), (95% CI) [1]	0.875 (0.594, 1.288)	
P-value [2]	0.4988	
p-value of Treatment*Cardiac Subpopulation [3]	0.5579	

N1 = Patients with missing postbaseline values due to COVID-19 or after initiation of local standard treatment for hATTR amyloidosis were included in analysis.
[1] Based on unstratified analysis.
In estimation of the odds ratio and relative risk, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the percentage difference or p-value.
[2] p-value based on the Wald test testing whether the relative risk equals to 1.
[3] p-value from a logistic regression using the penalized likelihood estimation (the FIRTH option) and with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Table 2.4
Modified Neuropathy Impairment Score +7 (mNIS+7)
Binary Subgroup Analysis
mITT Population

Month 18

Analysis Visit Statistics	Vutrisiran (HELIOS-A) (N=122)	Patisiran (HELIOS-A) (N=42)
Cardiac Subpopulation		
Yes		
Patients included in analysis, N1	40	14
<0 point increase from baseline, n(%)	16 (40.0)	4 (28.6)
≥0 point increase from baseline, n(%)	21 (52.5)	9 (64.3)
Missing, n(%)	3 (7.5)	1 (7.1)
<0 point increase from baseline, (95% CI)	40.0 (24.8, 55.2)	28.6 (4.9, 52.2)
Percentage difference (Vutrisiran – Patisiran), (95% CI)	11.429 (-16.687, 39.544)	
Odds ratio (Vutrisiran/Patisiran), (95% CI) [1]	1.667 (0.445, 6.244)	
Relative risk (Vutrisiran/Patisiran), (95% CI) [1]	1.400 (0.563, 3.482)	
P-value [2]	0.4692	

N1 = Patients with missing postbaseline values due to COVID-19 or after initiation of local standard treatment for hATTR amyloidosis were included in analysis.
[1] Based on unstratified analysis.
In estimation of the odds ratio and relative risk, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the percentage difference or p-value.
[2] p-value based on the Wald test testing whether the relative risk equals to 1.
[3] p-value from a logistic regression using the penalized likelihood estimation (the FIRTH option) and with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Table 2.4
Modified Neuropathy Impairment Score +7 (mNIS+7)
Binary Subgroup Analysis
mITT Population

Month 18

Analysis Visit Statistics	Vutrisiran (HELIOS-A) (N=122)	Patisiran (HELIOS-A) (N=42)
No		
Patients included in analysis, N1	82	28
<0 point increase from baseline, n(%)	42 (51.2)	12 (42.9)
≥0 point increase from baseline, n(%)	36 (43.9)	11 (39.3)
Missing, n(%)	4 (4.9)	5 (17.9)
<0 point increase from baseline, (95% CI)	51.2 (40.4, 62.0)	42.9 (24.5, 61.2)
Percentage difference (Vutrisiran – Patisiran), (95% CI)	8.362 (-12.922, 29.647)	
Odds ratio (Vutrisiran/Patisiran), (95% CI) [1]	1.400 (0.590, 3.324)	
Relative risk (Vutrisiran/Patisiran), (95% CI) [1]	1.195 (0.742, 1.926)	
P-value [2]	0.4639	
p-value of Treatment*Cardiac Subpopulation [3]	0.8745	

N1 = Patients with missing postbaseline values due to COVID-19 or after initiation of local standard treatment for hATTR amyloidosis were included in analysis.
[1] Based on unstratified analysis.
In estimation of the odds ratio and relative risk, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the percentage difference or p-value.
[2] p-value based on the Wald test testing whether the relative risk equals to 1.
[3] p-value from a logistic regression using the penalized likelihood estimation (the FIRTH option) and with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Table 2.4
Modified Neuropathy Impairment Score +7 (mNIS+7)
Binary Subgroup Analysis
mITT Population

Month 9

Analysis Visit Statistics	Vutrisiran (HELIOS-A) (N=122)	Patisiran (HELIOS-A) (N=42)
Weight (kg)		
<65 kg		
Patients included in analysis, N1	46	15
<0 point increase from baseline, n(%)	27 (58.7)	9 (60.0)
≥0 point increase from baseline, n(%)	17 (37.0)	6 (40.0)
Missing, n(%)	2 (4.3)	0
<0 point increase from baseline, (95% CI)	58.7 (44.5, 72.9)	60.0 (35.2, 84.8)
Percentage difference (Vutrisiran – Patisiran), (95% CI)	-1.304 (-29.889, 27.281)	
Odds ratio (Vutrisiran/Patisiran), (95% CI) [1]	0.947 (0.289, 3.108)	
Relative risk (Vutrisiran/Patisiran), (95% CI) [1]	0.978 (0.606, 1.579)	
P-value [2]	0.9283	

N1 = Patients with missing postbaseline values due to COVID-19 or after initiation of local standard treatment for hATTR amyloidosis were included in analysis.
[1] Based on unstratified analysis.
In estimation of the odds ratio and relative risk, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the percentage difference or p-value.
[2] p-value based on the Wald test testing whether the relative risk equals to 1.
[3] p-value from a logistic regression using the penalized likelihood estimation (the FIRTH option) and with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Table 2.4
Modified Neuropathy Impairment Score +7 (mNIS+7)
Binary Subgroup Analysis
mITT Population

Month 9

Analysis Visit Statistics	Vutrisiran (HELIOS-A) (N=122)	Patisiran (HELIOS-A) (N=42)
≥65 kg		
Patients included in analysis, N1	76	27
<0 point increase from baseline, n(%)	33 (43.4)	13 (48.1)
≥0 point increase from baseline, n(%)	40 (52.6)	12 (44.4)
Missing, n(%)	3 (3.9)	2 (7.4)
<0 point increase from baseline, (95% CI)	43.4 (32.3, 54.6)	48.1 (29.3, 67.0)
Percentage difference (Vutrisiran – Patisiran), (95% CI)	-4.727 (-26.622, 17.168)	
Odds ratio (Vutrisiran/Patisiran), (95% CI) [1]	0.826 (0.343, 1.994)	
Relative risk (Vutrisiran/Patisiran), (95% CI) [1]	0.902 (0.565, 1.440)	
P-value [2]	0.6652	
p-value of Treatment*Weight (kg) [3]	0.8381	

N1 = Patients with missing postbaseline values due to COVID-19 or after initiation of local standard treatment for hATTR amyloidosis were included in analysis.
[1] Based on unstratified analysis.
In estimation of the odds ratio and relative risk, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the percentage difference or p-value.
[2] p-value based on the Wald test testing whether the relative risk equals to 1.
[3] p-value from a logistic regression using the penalized likelihood estimation (the FIRTH option) and with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Table 2.4
Modified Neuropathy Impairment Score +7 (mNIS+7)
Binary Subgroup Analysis
mITT Population

Month 18

Analysis Visit Statistics	Vutrisiran (HELIOS-A) (N=122)	Patisiran (HELIOS-A) (N=42)
Weight (kg)		
<65 kg		
Patients included in analysis, N1	46	15
<0 point increase from baseline, n(%)	18 (39.1)	7 (46.7)
≥0 point increase from baseline, n(%)	24 (52.2)	6 (40.0)
Missing, n(%)	4 (8.7)	2 (13.3)
<0 point increase from baseline, (95% CI)	39.1 (25.0, 53.2)	46.7 (21.4, 71.9)
Percentage difference (Vutrisiran – Patisiran), (95% CI)	-7.536 (-36.455, 21.383)	
Odds ratio (Vutrisiran/Patisiran), (95% CI) [1]	0.735 (0.227, 2.378)	
Relative risk (Vutrisiran/Patisiran), (95% CI) [1]	0.839 (0.438, 1.606)	
P-value [2]	0.5954	

N1 = Patients with missing postbaseline values due to COVID-19 or after initiation of local standard treatment for hATTR amyloidosis were included in analysis.
[1] Based on unstratified analysis.
In estimation of the odds ratio and relative risk, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the percentage difference or p-value.
[2] p-value based on the Wald test testing whether the relative risk equals to 1.
[3] p-value from a logistic regression using the penalized likelihood estimation (the FIRTH option) and with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Table 2.4
Modified Neuropathy Impairment Score +7 (mNIS+7)
Binary Subgroup Analysis
mITT Population

Month 18

Analysis Visit Statistics	Vutrisiran (HELIOS-A) (N=122)	Patisiran (HELIOS-A) (N=42)
≥65 kg		
Patients included in analysis, N1	76	27
<0 point increase from baseline, n(%)	40 (52.6)	9 (33.3)
≥0 point increase from baseline, n(%)	33 (43.4)	14 (51.9)
Missing, n(%)	3 (3.9)	4 (14.8)
<0 point increase from baseline, (95% CI)	52.6 (41.4, 63.9)	33.3 (15.6, 51.1)
Percentage difference (Vutrisiran – Patisiran), (95% CI)	19.298 (-1.730, 40.326)	
Odds ratio (Vutrisiran/Patisiran), (95% CI) [1]	2.222 (0.887, 5.566)	
Relative risk (Vutrisiran/Patisiran), (95% CI) [1]	1.579 (0.889, 2.805)	
P-value [2]	0.1192	
p-value of Treatment*Weight (kg) [3]	0.1561	

N1 = Patients with missing postbaseline values due to COVID-19 or after initiation of local standard treatment for hATTR amyloidosis were included in analysis.
[1] Based on unstratified analysis.
In estimation of the odds ratio and relative risk, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the percentage difference or p-value.
[2] p-value based on the Wald test testing whether the relative risk equals to 1.
[3] p-value from a logistic regression using the penalized likelihood estimation (the FIRTH option) and with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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mNIS+7 – Domäne NIS-*Weakness*

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Table 2.6
Modified Neuropathy Impairment Score +7 (mNIS+7) Component Scores: Change from Baseline to Month 18, MMRM Model
Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A) Subgroup Analysis
mITT Population

Neuropathy Impairment Score - Weakness (NIS-W)

Subgroup Visit	LS Mean (95% CI) Vutrisiran (HELIOS-A) (N=122)	LS Mean (95% CI) Patisiran (HELIOS-A) (N=42)	LS Mean Difference (Vutrisiran-Patisiran) (95% CI), p-value	Standardized Effect Size (95% CI)
Age (years)				
<65	75	30		
Month 9	-0.34 (-2.09, 1.41)	-0.15 (-2.91, 2.61)	-0.19 (-3.45, 3.07), 0.9075	-0.03 (-0.45, 0.39)
Month 18	1.67 (-0.61, 3.95)	1.12 (-2.70, 4.95)	0.55 (-3.91, 5.00), 0.8092	0.04 (-0.39, 0.48)
≥65	44	10		
Month 9	-0.18 (-2.46, 2.10)	-1.25 (-6.04, 3.54)	1.07 (-4.23, 6.37), 0.6913	0.12 (-0.55, 0.80)
Month 18	1.83 (-0.88, 4.54)	0.03 (-5.44, 5.49)	1.80 (-4.29, 7.90), 0.5598	0.22 (-0.49, 0.94)
p-value of Treatment*Age	0.6896			

mNIS+7 score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurologic impairment (range = 0 to 304). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.
LS estimates and p-value derived from mixed-effects model for repeated measures (MMRM), controlling for categorical factors (treatment, visit), the subgroup variable, continuous covariate (baseline value), and interaction (treatment by visit, treatment by subgroup).
Standardized effect size (d) = LS mean difference/estimated pooled standard deviation with the small sample bias correction.

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Table 2.6
Modified Neuropathy Impairment Score +7 (mNIS+7) Component Scores: Change from Baseline to Month 18, MMRM Model
Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A) Subgroup Analysis
mITT Population

Neuropathy Impairment Score - Weakness (NIS-W)

Subgroup Visit	LS Mean (95% CI) Vutrisiran (HELIOS-A) (N=122)	LS Mean (95% CI) Patisiran (HELIOS-A) (N=42)	LS Mean Difference (Vutrisiran-Patisiran) (95% CI), p-value	Standardized Effect Size (95% CI)
Sex				
Male	77	25		
Month 9	-0.17 (-1.90, 1.56)	-0.21 (-3.22, 2.81)	0.04 (-3.44, 3.51), 0.9831	0.01 (-0.44, 0.45)
Month 18	1.84 (-0.42, 4.11)	1.07 (-2.95, 5.08)	0.78 (-3.84, 5.39), 0.7406	0.08 (-0.39, 0.55)
Female	42	15		
Month 9	-0.50 (-2.86, 1.86)	-0.79 (-4.68, 3.10)	0.29 (-4.26, 4.84), 0.8992	0.03 (-0.55, 0.61)
Month 18	1.51 (-1.25, 4.28)	0.48 (-4.21, 5.17)	1.03 (-4.42, 6.48), 0.7097	0.08 (-0.52, 0.68)
p-value of Treatment*Sex	0.9300			

mNIS+7 score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurologic impairment (range = 0 to 304). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.
LS estimates and p-value derived from mixed-effects model for repeated measures (MMRM), controlling for categorical factors (treatment, visit), the subgroup variable, continuous covariate (baseline value), and interaction (treatment by visit, treatment by subgroup).
Standardized effect size (d) = LS mean difference/estimated pooled standard deviation with the small sample bias correction.

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Table 2.6
Modified Neuropathy Impairment Score +7 (mNIS+7) Component Scores: Change from Baseline to Month 18, MMRM Model
Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A) Subgroup Analysis
mITT Population

Neuropathy Impairment Score - Weakness (NIS-W)

Subgroup Visit	LS Mean (95% CI) Vutrisiran (HELIOS-A) (N=122)	LS Mean (95% CI) Patisiran (HELIOS-A) (N=42)	LS Mean Difference (Vutrisiran-Patisiran) (95% CI), p-value	Standardized Effect Size (95% CI)
Race				
White	84	28		
Month 9	-0.98 (-2.61, 0.64)	0.87 (-1.93, 3.68)	-1.86 (-5.10, 1.39), 0.2599	-0.25 (-0.67, 0.18)
Month 18	1.02 (-1.16, 3.20)	2.15 (-1.69, 6.00)	-1.13 (-5.55, 3.29), 0.6140	-0.10 (-0.54, 0.35)
All Other Races	35	12		
Month 9	1.42 (-1.10, 3.94)	-3.45 (-7.72, 0.83)	4.87 (-0.09, 9.83), 0.0544	0.65 (-0.01, 1.31)
Month 18	3.43 (0.53, 6.33)	-2.17 (-7.17, 2.84)	5.59 (-0.19, 11.38), 0.0580	0.56 (-0.12, 1.24)
p-value of Treatment*Race	0.0260			

mNIS+7 score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurologic impairment (range = 0 to 304). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.
LS estimates and p-value derived from mixed-effects model for repeated measures (MMRM), controlling for categorical factors (treatment, visit), the subgroup variable, continuous covariate (baseline value), and interaction (treatment by visit, treatment by subgroup).
Standardized effect size (d) = LS mean difference/estimated pooled standard deviation with the small sample bias correction.

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Table 2.6
Modified Neuropathy Impairment Score +7 (mNIS+7) Component Scores: Change from Baseline to Month 18, MMRM Model
Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A) Subgroup Analysis
mITT Population

Neuropathy Impairment Score - Weakness (NIS-W)

Subgroup Visit	LS Mean (95% CI) Vutrisiran (HELIOS-A) (N=122)	LS Mean (95% CI) Patisiran (HELIOS-A) (N=42)	LS Mean Difference (Vutrisiran-Patisiran) (95% CI), p-value	Standardized Effect Size (95% CI)
Region				
North America	27	8		
Month 9	-1.56 (-4.63, 1.51)	-2.03 (-7.38, 3.32)	0.47 (-5.62, 6.56), 0.8793	0.09 (-0.69, 0.86)
Month 18	0.46 (-2.91, 3.83)	-0.76 (-6.74, 5.21)	1.22 (-5.56, 8.01), 0.7224	0.17 (-0.69, 1.04)
Western Europe	40	18		
Month 9	0.04 (-2.34, 2.42)	-1.23 (-4.79, 2.32)	1.28 (-3.00, 5.55), 0.5559	0.17 (-0.38, 0.72)
Month 18	2.07 (-0.72, 4.85)	0.03 (-4.37, 4.43)	2.03 (-3.17, 7.24), 0.4422	0.30 (-0.26, 0.87)
Rest of World	52	14		
Month 9	0.08 (-2.03, 2.20)	1.52 (-2.50, 5.55)	-1.44 (-5.98, 3.09), 0.5305	-0.17 (-0.75, 0.42)
Month 18	2.11 (-0.47, 4.68)	2.79 (-2.00, 7.58)	-0.69 (-6.11, 4.74), 0.8030	-0.05 (-0.65, 0.56)
p-value of Treatment*Region	0.6824			

mNIS+7 score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurologic impairment (range = 0 to 304). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.
LS estimates and p-value derived from mixed-effects model for repeated measures (MMRM), controlling for categorical factors (treatment, visit), the subgroup variable, continuous covariate (baseline value), and interaction (treatment by visit, treatment by subgroup).
Standardized effect size (d) = LS mean difference/estimated pooled standard deviation with the small sample bias correction.

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Table 2.6
Modified Neuropathy Impairment Score +7 (mNIS+7) Component Scores: Change from Baseline to Month 18, MMRM Model
Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A) Subgroup Analysis
mITT Population

Neuropathy Impairment Score - Weakness (NIS-W)

Subgroup Visit	LS Mean (95% CI) Vutrisiran (HELIOS-A) (N=122)	LS Mean (95% CI) Patisiran (HELIOS-A) (N=42)	LS Mean Difference (Vutrisiran-Patisiran) (95% CI), p-value	Standardized Effect Size (95% CI)
Baseline NIS				
<50	77	27		
Month 9	-1.45 (-3.67, 0.77)	-2.67 (-5.76, 0.42)	1.22 (-2.11, 4.55), 0.4701	0.23 (-0.20, 0.67)
Month 18	0.56 (-2.10, 3.22)	-1.39 (-5.44, 2.67)	1.94 (-2.55, 6.44), 0.3943	0.23 (-0.22, 0.68)
≥50	42	13		
Month 9	1.75 (-1.65, 5.15)	4.17 (-0.55, 8.89)	-2.42 (-7.14, 2.30), 0.3129	-0.23 (-0.84, 0.39)
Month 18	3.76 (0.07, 7.45)	5.46 (0.05, 10.87)	-1.70 (-7.29, 3.90), 0.5508	-0.11 (-0.77, 0.54)
p-value of Treatment*Baseline NIS	0.2143			

mNIS+7 score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurologic impairment (range = 0 to 304). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.
LS estimates and p-value derived from mixed-effects model for repeated measures (MMRM), controlling for categorical factors (treatment, visit), the subgroup variable, continuous covariate (baseline value), and interaction (treatment by visit, treatment by subgroup).
Standardized effect size (d) = LS mean difference/estimated pooled standard deviation with the small sample bias correction.

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Table 2.6
Modified Neuropathy Impairment Score +7 (mNIS+7) Component Scores: Change from Baseline to Month 18, MMRM Model
Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A) Subgroup Analysis
mITT Population

Neuropathy Impairment Score - Weakness (NIS-W)

Subgroup Visit	LS Mean (95% CI) Vutrisiran (HELIOS-A) (N=122)	LS Mean (95% CI) Patisiran (HELIOS-A) (N=42)	LS Mean Difference (Vutrisiran-Patisiran) (95% CI), p-value	Standardized Effect Size (95% CI)
Previous Tetramer Stabilizer Use				
Yes	74	32		
Month 9	-0.54 (-2.29, 1.21)	-0.12 (-2.78, 2.55)	-0.43 (-3.61, 2.76), 0.7922	-0.05 (-0.46, 0.36)
Month 18	1.46 (-0.83, 3.76)	1.16 (-2.60, 4.91)	0.31 (-4.09, 4.71), 0.8901	0.02 (-0.40, 0.45)
No	45	8		
Month 9	0.15 (-2.13, 2.43)	-1.66 (-6.98, 3.66)	1.81 (-3.96, 7.59), 0.5359	0.29 (-0.45, 1.04)
Month 18	2.16 (-0.53, 4.85)	-0.39 (-6.33, 5.55)	2.55 (-3.96, 9.05), 0.4412	0.36 (-0.43, 1.15)
p-value of Treatment*Previous Tetramer Stabilizer Use	0.5025			

mNIS+7 score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurologic impairment (range = 0 to 304). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.
LS estimates and p-value derived from mixed-effects model for repeated measures (MMRM), controlling for categorical factors (treatment, visit), the subgroup variable, continuous covariate (baseline value), and interaction (treatment by visit, treatment by subgroup).
Standardized effect size (d) = LS mean difference/estimated pooled standard deviation with the small sample bias correction.

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Table 2.6
Modified Neuropathy Impairment Score +7 (mNIS+7) Component Scores: Change from Baseline to Month 18, MMRM Model
Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A) Subgroup Analysis
mITT Population

Neuropathy Impairment Score - Weakness (NIS-W)

Subgroup Visit	LS Mean (95% CI) Vutrisiran (HELIOS-A) (N=122)	LS Mean (95% CI) Patisiran (HELIOS-A) (N=42)	LS Mean Difference (Vutrisiran-Patisiran) (95% CI), p-value	Standardized Effect Size (95% CI)
Genotype				
V30M	53	20		
Month 9	0.01 (-2.05, 2.07)	-2.29 (-5.64, 1.05)	2.30 (-1.63, 6.23), 0.2491	0.36 (-0.15, 0.87)
Month 18	2.02 (-0.51, 4.54)	-1.01 (-5.26, 3.25)	3.02 (-1.93, 7.97), 0.2297	0.46 (-0.07, 0.98)
non-V30M	66	20		
Month 9	-0.51 (-2.36, 1.34)	1.45 (-1.90, 4.80)	-1.96 (-5.78, 1.86), 0.3128	-0.23 (-0.73, 0.27)
Month 18	1.50 (-0.86, 3.86)	2.74 (-1.54, 7.01)	-1.24 (-6.12, 3.64), 0.6176	-0.09 (-0.62, 0.44)
p-value of Treatment*Genotype	0.1260			

mNIS+7 score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurologic impairment (range = 0 to 304). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.
LS estimates and p-value derived from mixed-effects model for repeated measures (MMRM), controlling for categorical factors (treatment, visit), the subgroup variable, continuous covariate (baseline value), and interaction (treatment by visit, treatment by subgroup).
Standardized effect size (d) = LS mean difference/estimated pooled standard deviation with the small sample bias correction.

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Table 2.6
Modified Neuropathy Impairment Score +7 (mNIS+7) Component Scores: Change from Baseline to Month 18, MMRM Model
Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A) Subgroup Analysis
mITT Population

Neuropathy Impairment Score - Weakness (NIS-W)

Subgroup Visit	LS Mean (95% CI) Vutrisiran (HELIOS-A) (N=122)	LS Mean (95% CI) Patisiran (HELIOS-A) (N=42)	LS Mean Difference (Vutrisiran-Patisiran) (95% CI), p-value	Standardized Effect Size (95% CI)
FAP Stage				
I	83	30		
Month 9	-0.76 (-2.51, 1.00)	-0.44 (-3.25, 2.36)	-0.31 (-3.52, 2.90), 0.8488	-0.04 (-0.46, 0.37)
Month 18	1.26 (-1.03, 3.54)	0.83 (-3.02, 4.67)	0.43 (-3.97, 4.83), 0.8471	0.04 (-0.38, 0.46)
II&III	36	10		
Month 9	0.78 (-2.01, 3.56)	-0.38 (-5.38, 4.62)	1.16 (-4.23, 6.55), 0.6715	0.13 (-0.56, 0.82)
Month 18	2.79 (-0.36, 5.94)	0.89 (-4.79, 6.57)	1.90 (-4.30, 8.10), 0.5463	0.22 (-0.58, 1.01)
p-value of Treatment*FAP Stage	0.6433			

mNIS+7 score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurologic impairment (range = 0 to 304). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.
LS estimates and p-value derived from mixed-effects model for repeated measures (MMRM), controlling for categorical factors (treatment, visit), the subgroup variable, continuous covariate (baseline value), and interaction (treatment by visit, treatment by subgroup).
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Table 2.6
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Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A) Subgroup Analysis
mITT Population

Neuropathy Impairment Score - Weakness (NIS-W)

Subgroup Visit	LS Mean (95% CI) Vutrisiran (HELIOS-A) (N=122)	LS Mean (95% CI) Patisiran (HELIOS-A) (N=42)	LS Mean Difference (Vutrisiran-Patisiran) (95% CI), p-value	Standardized Effect Size (95% CI)
Cardiac Subpopulation				
Yes	38	14		
Month 9	-0.30 (-2.60, 2.00)	7.17 (3.43, 10.92)	-7.47 (-11.83, -3.11), 0.0009	-0.88 (-1.51, -0.25)
Month 18	1.72 (-1.04, 4.47)	8.42 (3.79, 13.05)	-6.70 (-12.07, -1.34), 0.0145	-0.42 (-1.04, 0.21)
No	81	26		
Month 9	-0.29 (-1.88, 1.29)	-4.52 (-7.27, -1.78)	4.23 (1.08, 7.39), 0.0089	0.67 (0.22, 1.12)
Month 18	1.72 (-0.47, 3.91)	-3.27 (-7.15, 0.61)	5.00 (0.55, 9.44), 0.0277	0.68 (0.21, 1.16)
p-value of Treatment*Cardiac Subpopulation	3.049E-05			

mNIS+7 score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurologic impairment (range = 0 to 304). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.
LS estimates and p-value derived from mixed-effects model for repeated measures (MMRM), controlling for categorical factors (treatment, visit), the subgroup variable, continuous covariate (baseline value), and interaction (treatment by visit, treatment by subgroup).
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Table 2.6
Modified Neuropathy Impairment Score +7 (mNIS+7) Component Scores: Change from Baseline to Month 18, MMRM Model
Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A) Subgroup Analysis
mITT Population

Neuropathy Impairment Score - Weakness (NIS-W)

Subgroup Visit	LS Mean (95% CI) Vutrisiran (HELIOS-A) (N=122)	LS Mean (95% CI) Patisiran (HELIOS-A) (N=42)	LS Mean Difference (Vutrisiran-Patisiran) (95% CI), p-value	Standardized Effect Size (95% CI)
Weight (kg)				
<65	44	15		
Month 9	0.14 (-2.16, 2.43)	0.93 (-2.94, 4.81)	-0.79 (-5.29, 3.71), 0.7283	-0.08 (-0.66, 0.49)
Month 18	2.15 (-0.58, 4.88)	2.21 (-2.49, 6.90)	-0.05 (-5.48, 5.38), 0.9846	-0.00 (-0.62, 0.61)
≥65	75	25		
Month 9	-0.54 (-2.32, 1.23)	-1.24 (-4.25, 1.77)	0.70 (-2.79, 4.19), 0.6921	0.11 (-0.34, 0.56)
Month 18	1.47 (-0.82, 3.77)	0.04 (-3.97, 4.04)	1.44 (-3.17, 6.05), 0.5389	0.16 (-0.31, 0.62)
p-value of Treatment*Weight	0.6050			

mNIS+7 score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurologic impairment (range = 0 to 304). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.
LS estimates and p-value derived from mixed-effects model for repeated measures (MMRM), controlling for categorical factors (treatment, visit), the subgroup variable, continuous covariate (baseline value), and interaction (treatment by visit, treatment by subgroup).
Standardized effect size (d) = LS mean difference/estimated pooled standard deviation with the small sample bias correction.

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Table 2.8
Modified Neuropathy Impairment Score +7 (mNIS+7) Components: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Component: Neuropathy Impairment Score - Weakness (NIS-W)

Age (years): <65

Subgroup Visit	Vutrisiran (HELIOS-A) (N=76)	Patisiran (HELIOS-A) (N=31)
Baseline		
n	76	31
Mean (SD)	19.70 (19.74)	17.89 (15.54)
SE	2.26	2.79
Median	11.75	12.50
Min, Max	0.0, 86.0	0.0, 52.4
Month 9		
Actual Value		
n	74	30
Mean (SD)	18.90 (20.07)	17.68 (18.49)
SE	2.33	3.38
Median	12.25	11.50
Min, Max	0.0, 89.1	0.0, 69.6
Change from baseline		
n	74	30
Mean (SD)	-0.28 (5.42)	0.10 (10.15)
SE	0.63	1.85
Median	0.00	-0.94
Min, Max	-16.0, 17.0	-17.3, 46.4

mNIS+7 score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurologic impairment (range = 0 to 304). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 2.8
Modified Neuropathy Impairment Score +7 (mNIS+7) Components: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Component: Neuropathy Impairment Score - Weakness (NIS-W)

Age (years): <65

Subgroup Visit	Vutrisiran (HELIOS-A) (N=76)	Patisiran (HELIOS-A) (N=31)
Month 18		
Actual Value		
n	74	27
Mean (SD)	21.29 (22.24)	17.81 (22.73)
SE	2.59	4.37
Median	13.94	10.50
Min, Max	0.0, 101.3	0.0, 97.4
Change from baseline		
n	74	27
Mean (SD)	2.14 (9.78)	1.40 (17.47)
SE	1.14	3.36
Median	0.75	-0.50
Min, Max	-14.0, 59.5	-39.5, 74.1

mNIS+7 score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurologic impairment (range = 0 to 304). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 2.8
Modified Neuropathy Impairment Score +7 (mNIS+7) Components: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Component: Neuropathy Impairment Score - Weakness (NIS-W)

Age (years): ≥65

Subgroup Visit	Vutrisiran (HELIOS-A) (N=46)	Patisiran (HELIOS-A) (N=11)
Baseline		
n	46	11
Mean (SD)	22.85 (19.67)	31.73 (23.68)
SE	2.90	7.14
Median	14.50	24.00
Min, Max	0.0, 72.9	0.0, 66.9
Month 9		
Actual Value		
n	43	10
Mean (SD)	21.83 (18.30)	28.39 (25.31)
SE	2.79	8.00
Median	16.25	24.44
Min, Max	0.0, 60.3	0.0, 80.0
Change from baseline		
n	43	10
Mean (SD)	-0.06 (7.26)	-1.91 (14.21)
SE	1.11	4.49
Median	0.00	1.00
Min, Max	-20.3, 15.9	-23.5, 16.0

mNIS+7 score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurologic impairment (range = 0 to 304). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

Alnylam Pharmaceuticals Inc.
ALN-TTRSC02-002

Table 2.8
Modified Neuropathy Impairment Score +7 (mNIS+7) Components: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Component: Neuropathy Impairment Score - Weakness (NIS-W)

Age (years): ≥65

Subgroup Visit	Vutrisiran (HELIOS-A) (N=46)	Patisiran (HELIOS-A) (N=11)
Month 18		
Actual Value		
n	41	9
Mean (SD)	23.93 (21.76)	31.61 (21.81)
SE	3.40	7.27
Median	20.50	23.00
Min, Max	0.0, 82.4	3.0, 71.5
Change from baseline		
n	41	9
Mean (SD)	0.88 (7.67)	0.56 (9.48)
SE	1.20	3.16
Median	1.50	3.00
Min, Max	-13.9, 18.0	-20.9, 10.0

mNIS+7 score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurologic impairment (range = 0 to 304). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Alnylam Pharmaceuticals Inc.
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Table 2.8
Modified Neuropathy Impairment Score +7 (mNIS+7) Components: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Component: Neuropathy Impairment Score - Weakness (NIS-W)

Sex: Male

Subgroup Visit	Vutrisiran (HELIOS-A) (N=79)	Patisiran (HELIOS-A) (N=27)
Baseline		
n	79	27
Mean (SD)	23.30 (20.46)	21.51 (17.70)
SE	2.30	3.41
Median	16.75	19.75
Min, Max	0.0, 86.0	0.0, 66.9
Month 9		
Actual Value		
n	76	25
Mean (SD)	22.46 (21.08)	20.16 (17.42)
SE	2.42	3.48
Median	18.44	17.50
Min, Max	0.0, 89.1	0.0, 59.3
Change from baseline		
n	76	25
Mean (SD)	-0.28 (6.47)	-0.15 (7.35)
SE	0.74	1.47
Median	0.63	-0.50
Min, Max	-20.3, 17.0	-19.9, 16.0

mNIS+7 score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurologic impairment (range = 0 to 304). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 2.8
Modified Neuropathy Impairment Score +7 (mNIS+7) Components: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Component: Neuropathy Impairment Score - Weakness (NIS-W)

Sex: Male

Subgroup Visit	Vutrisiran (HELIOS-A) (N=79)	Patisiran (HELIOS-A) (N=27)
Month 18		
Actual Value		
n	74	22
Mean (SD)	24.43 (23.66)	19.78 (17.74)
SE	2.75	3.78
Median	17.69	16.81
Min, Max	0.0, 101.3	0.0, 71.4
Change from baseline		
n	74	22
Mean (SD)	1.62 (10.05)	1.27 (7.38)
SE	1.17	1.57
Median	1.31	0.00
Min, Max	-14.0, 59.5	-20.9, 19.0

mNIS+7 score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurologic impairment (range = 0 to 304). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 2.8
Modified Neuropathy Impairment Score +7 (mNIS+7) Components: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Component: Neuropathy Impairment Score - Weakness (NIS-W)

Sex: Female

Subgroup Visit	Vutrisiran (HELIOS-A) (N=43)	Patisiran (HELIOS-A) (N=15)
Baseline		
n	43	15
Mean (SD)	16.46 (17.58)	21.52 (21.14)
SE	2.68	5.46
Median	8.00	17.50
Min, Max	0.0, 72.9	0.0, 66.1
Month 9		
Actual Value		
n	41	15
Mean (SD)	15.37 (15.03)	20.68 (25.71)
SE	2.35	6.64
Median	13.00	10.50
Min, Max	0.0, 56.1	0.0, 80.0
Change from baseline		
n	41	15
Mean (SD)	-0.05 (5.52)	-0.84 (15.89)
SE	0.86	4.10
Median	0.00	-2.50
Min, Max	-16.8, 11.5	-23.5, 46.4

mNIS+7 score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurologic impairment (range = 0 to 304). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 2.8
Modified Neuropathy Impairment Score +7 (mNIS+7) Components: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Component: Neuropathy Impairment Score - Weakness (NIS-W)

Sex: Female

Subgroup Visit	Vutrisiran (HELIOS-A) (N=43)	Patisiran (HELIOS-A) (N=15)
Month 18		
Actual Value		
n	41	14
Mean (SD)	18.25 (18.27)	23.58 (30.12)
SE	2.85	8.05
Median	11.00	8.50
Min, Max	0.0, 82.4	0.0, 97.4
Change from baseline		
n	41	14
Mean (SD)	1.82 (7.07)	1.06 (24.04)
SE	1.10	6.43
Median	1.00	-1.44
Min, Max	-11.0, 18.0	-39.5, 74.1

mNIS+7 score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurologic impairment (range = 0 to 304). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 2.8
Modified Neuropathy Impairment Score +7 (mNIS+7) Components: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Component: Neuropathy Impairment Score - Weakness (NIS-W)

Race: White

Subgroup Visit	Vutrisiran (HELIOS-A) (N=86)	Patisiran (HELIOS-A) (N=29)
Baseline		
n	86	29
Mean (SD)	20.71 (19.08)	21.03 (18.07)
SE	2.06	3.35
Median	13.44	17.50
Min, Max	0.0, 72.9	0.0, 66.1
Month 9		
Actual Value		
n	83	28
Mean (SD)	19.24 (18.42)	20.96 (21.68)
SE	2.02	4.10
Median	13.50	11.50
Min, Max	0.0, 67.5	0.0, 80.0
Change from baseline		
n	83	28
Mean (SD)	-0.90 (5.46)	0.82 (11.94)
SE	0.60	2.26
Median	0.00	0.00
Min, Max	-16.8, 11.0	-23.5, 46.4

mNIS+7 score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurologic impairment (range = 0 to 304). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 2.8
Modified Neuropathy Impairment Score +7 (mNIS+7) Components: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Component: Neuropathy Impairment Score - Weakness (NIS-W)

Race: White

Subgroup Visit	Vutrisiran (HELIOS-A) (N=86)	Patisiran (HELIOS-A) (N=29)
Month 18		
Actual Value		
n	82	25
Mean (SD)	21.54 (20.86)	22.84 (24.80)
SE	2.30	4.96
Median	14.25	16.00
Min, Max	0.0, 82.4	0.0, 97.4
Change from baseline		
n	82	25
Mean (SD)	1.30 (9.45)	3.66 (16.05)
SE	1.04	3.21
Median	0.50	0.00
Min, Max	-14.0, 59.5	-16.5, 74.1

mNIS+7 score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurologic impairment (range = 0 to 304). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 2.8
Modified Neuropathy Impairment Score +7 (mNIS+7) Components: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Component: Neuropathy Impairment Score - Weakness (NIS-W)

Race: All Other Races

Subgroup Visit	Vutrisiran (HELIOS-A) (N=36)	Patisiran (HELIOS-A) (N=13)
Baseline		
n	36	13
Mean (SD)	21.33 (21.38)	22.58 (20.91)
SE	3.56	5.80
Median	10.50	23.50
Min, Max	0.0, 86.0	0.0, 66.9
Month 9		
Actual Value		
n	34	12
Mean (SD)	21.78 (21.83)	18.93 (18.63)
SE	3.74	5.38
Median	13.50	18.19
Min, Max	0.0, 89.1	0.0, 47.0
Change from baseline		
n	34	12
Mean (SD)	1.51 (7.33)	-3.27 (8.77)
SE	1.26	2.53
Median	1.25	-2.75
Min, Max	-20.3, 17.0	-19.9, 10.5

mNIS+7 score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurologic impairment (range = 0 to 304). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 2.8
Modified Neuropathy Impairment Score +7 (mNIS+7) Components: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Component: Neuropathy Impairment Score - Weakness (NIS-W)

Race: All Other Races

Subgroup Visit	Vutrisiran (HELIOS-A) (N=36)	Patisiran (HELIOS-A) (N=13)
Month 18		
Actual Value		
n	33	11
Mean (SD)	23.95 (24.90)	17.67 (18.86)
SE	4.33	5.69
Median	13.00	10.00
Min, Max	0.0, 101.3	0.0, 46.0
Change from baseline		
n	33	11
Mean (SD)	2.67 (8.08)	-4.41 (14.07)
SE	1.41	4.24
Median	1.50	-0.50
Min, Max	-13.9, 24.1	-39.5, 8.0

mNIS+7 score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurologic impairment (range = 0 to 304). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 2.8
Modified Neuropathy Impairment Score +7 (mNIS+7) Components: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Component: Neuropathy Impairment Score - Weakness (NIS-W)

Region: North America

Subgroup Visit	Vutrisiran (HELIOS-A) (N=27)	Patisiran (HELIOS-A) (N=8)
Baseline		
n	27	8
Mean (SD)	9.53 (12.25)	12.06 (13.10)
SE	2.36	4.63
Median	6.00	6.25
Min, Max	0.0, 44.5	0.0, 36.0
Month 9		
Actual Value		
n	25	8
Mean (SD)	6.81 (9.35)	10.98 (15.75)
SE	1.87	5.57
Median	2.50	6.00
Min, Max	0.0, 36.0	0.0, 46.5
Change from baseline		
n	25	8
Mean (SD)	-0.02 (4.94)	-1.08 (6.36)
SE	0.99	2.25
Median	0.00	0.00
Min, Max	-9.0, 10.0	-10.0, 10.5

mNIS+7 score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurologic impairment (range = 0 to 304). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 2.8
Modified Neuropathy Impairment Score +7 (mNIS+7) Components: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Component: Neuropathy Impairment Score - Weakness (NIS-W)

Region: North America

Subgroup Visit	Vutrisiran (HELIOS-A) (N=27)	Patisiran (HELIOS-A) (N=8)
Month 18		
Actual Value		
n	25	6
Mean (SD)	8.11 (13.70)	9.21 (16.79)
SE	2.74	6.86
Median	2.00	4.00
Min, Max	0.0, 47.0	0.0, 43.3
Change from baseline		
n	25	6
Mean (SD)	-1.90 (5.78)	-1.71 (7.85)
SE	1.16	3.21
Median	0.00	0.00
Min, Max	-14.0, 9.8	-16.5, 7.3

mNIS+7 score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurologic impairment (range = 0 to 304). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 2.8
Modified Neuropathy Impairment Score +7 (mNIS+7) Components: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Component: Neuropathy Impairment Score - Weakness (NIS-W)

Region: Western Europe

Subgroup Visit	Vutrisiran (HELIOS-A) (N=42)	Patisiran (HELIOS-A) (N=20)
Baseline		
n	42	20
Mean (SD)	21.24 (19.74)	23.58 (18.38)
SE	3.05	4.11
Median	14.31	18.63
Min, Max	0.0, 72.9	0.0, 66.1
Month 9		
Actual Value		
n	40	18
Mean (SD)	20.53 (17.55)	20.67 (19.81)
SE	2.77	4.67
Median	17.13	14.25
Min, Max	0.0, 56.1	0.0, 80.0
Change from baseline		
n	40	18
Mean (SD)	-0.09 (6.80)	-1.47 (10.13)
SE	1.08	2.39
Median	0.00	-0.50
Min, Max	-16.8, 15.9	-23.5, 16.0

mNIS+7 score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurologic impairment (range = 0 to 304). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 2.8
Modified Neuropathy Impairment Score +7 (mNIS+7) Components: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Component: Neuropathy Impairment Score - Weakness (NIS-W)

Region: Western Europe

Subgroup Visit	Vutrisiran (HELIOS-A) (N=42)	Patisiran (HELIOS-A) (N=20)
Month 18		
Actual Value		
n	40	17
Mean (SD)	24.06 (19.99)	21.88 (17.48)
SE	3.16	4.24
Median	20.63	17.63
Min, Max	0.0, 82.4	3.0, 71.5
Change from baseline		
n	40	17
Mean (SD)	3.44 (7.34)	1.15 (4.59)
SE	1.16	1.11
Median	3.31	-1.00
Min, Max	-13.6, 18.0	-5.3, 10.0

mNIS+7 score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurologic impairment (range = 0 to 304). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 2.8
Modified Neuropathy Impairment Score +7 (mNIS+7) Components: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Component: Neuropathy Impairment Score - Weakness (NIS-W)

Region: Rest of World

Subgroup Visit	Vutrisiran (HELIOS-A) (N=53)	Patisiran (HELIOS-A) (N=14)
Baseline		
n	53	14
Mean (SD)	26.40 (20.55)	23.96 (21.31)
SE	2.82	5.70
Median	28.50	23.56
Min, Max	0.0, 86.0	0.0, 66.9
Month 9		
Actual Value		
n	52	14
Mean (SD)	25.88 (21.44)	25.30 (23.34)
SE	2.97	6.24
Median	23.25	24.38
Min, Max	0.0, 89.1	0.0, 69.6
Change from baseline		
n	52	14
Mean (SD)	-0.37 (6.21)	1.34 (14.52)
SE	0.86	3.88
Median	0.25	-1.75
Min, Max	-20.3, 17.0	-19.9, 46.4

mNIS+7 score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurologic impairment (range = 0 to 304). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 2.8
Modified Neuropathy Impairment Score +7 (mNIS+7) Components: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Component: Neuropathy Impairment Score - Weakness (NIS-W)

Region: Rest of World

Subgroup Visit	Vutrisiran (HELIOS-A) (N=53)	Patisiran (HELIOS-A) (N=14)
Month 18		
Actual Value		
n	50	13
Mean (SD)	27.83 (24.09)	26.00 (30.35)
SE	3.41	8.42
Median	31.06	11.00
Min, Max	0.0, 101.3	0.0, 97.4
Change from baseline		
n	50	13
Mean (SD)	2.08 (11.08)	2.58 (25.72)
SE	1.57	7.13
Median	1.00	-0.50
Min, Max	-13.9, 59.5	-39.5, 74.1

mNIS+7 score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurologic impairment (range = 0 to 304). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 2.8
Modified Neuropathy Impairment Score +7 (mNIS+7) Components: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Component: Neuropathy Impairment Score - Weakness (NIS-W)

Baseline NIS: <50

Subgroup Visit	Vutrisiran (HELIOS-A) (N=78)	Patisiran (HELIOS-A) (N=27)
Baseline		
n	78	27
Mean (SD)	8.44 (8.27)	10.54 (9.51)
SE	0.94	1.83
Median	6.75	9.50
Min, Max	0.0, 34.0	0.0, 36.0
Month 9		
Actual Value		
n	77	27
Mean (SD)	8.66 (8.98)	9.42 (10.70)
SE	1.02	2.06
Median	6.00	7.00
Min, Max	0.0, 36.5	0.0, 46.5
Change from baseline		
n	77	27
Mean (SD)	0.55 (4.99)	-1.12 (5.77)
SE	0.57	1.11
Median	0.00	-0.50
Min, Max	-10.5, 15.9	-17.5, 10.5

mNIS+7 score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurologic impairment (range = 0 to 304). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 2.8
Modified Neuropathy Impairment Score +7 (mNIS+7) Components: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Component: Neuropathy Impairment Score - Weakness (NIS-W)

Baseline NIS: <50

Subgroup Visit	Vutrisiran (HELIOS-A) (N=78)	Patisiran (HELIOS-A) (N=27)
Month 18		
Actual Value		
n	75	25
Mean (SD)	9.67 (11.62)	10.51 (10.04)
SE	1.34	2.01
Median	6.00	10.00
Min, Max	0.0, 63.5	0.0, 43.3
Change from baseline		
n	75	25
Mean (SD)	1.44 (9.21)	0.37 (5.44)
SE	1.06	1.09
Median	0.50	0.00
Min, Max	-14.0, 59.5	-16.5, 10.0

mNIS+7 score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurologic impairment (range = 0 to 304). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 2.8
Modified Neuropathy Impairment Score +7 (mNIS+7) Components: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Component: Neuropathy Impairment Score - Weakness (NIS-W)

Baseline NIS: ≥50

Subgroup Visit	Vutrisiran (HELIOS-A) (N=44)	Patisiran (HELIOS-A) (N=15)
Baseline		
n	44	15
Mean (SD)	42.96 (13.75)	41.26 (14.54)
SE	2.07	3.75
Median	40.56	43.00
Min, Max	20.0, 86.0	23.3, 66.9
Month 9		
Actual Value		
n	40	13
Mean (SD)	41.76 (14.96)	43.06 (17.40)
SE	2.37	4.83
Median	39.50	40.00
Min, Max	17.8, 89.1	24.5, 80.0
Change from baseline		
n	40	13
Mean (SD)	-1.64 (7.75)	1.08 (18.09)
SE	1.22	5.02
Median	0.56	-2.50
Min, Max	-20.3, 17.0	-23.5, 46.4

mNIS+7 score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurologic impairment (range = 0 to 304). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

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Table 2.8
Modified Neuropathy Impairment Score +7 (mNIS+7) Components: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Component: Neuropathy Impairment Score - Weakness (NIS-W)

Baseline NIS: ≥50

Subgroup Visit	Vutrisiran (HELIOS-A) (N=44)	Patisiran (HELIOS-A) (N=15)
Month 18		
Actual Value		
n	40	11
Mean (SD)	45.78 (16.97)	45.68 (25.80)
SE	2.68	7.78
Median	42.13	40.63
Min, Max	18.4, 101.3	5.5, 97.4
Change from baseline		
n	40	11
Mean (SD)	2.16 (8.89)	3.07 (28.10)
SE	1.41	8.47
Median	2.44	-1.00
Min, Max	-13.9, 24.1	-39.5, 74.1

mNIS+7 score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurologic impairment (range = 0 to 304). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 2.8
Modified Neuropathy Impairment Score +7 (mNIS+7) Components: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Component: Neuropathy Impairment Score - Weakness (NIS-W)

Previous Tetramer Stabilizer Use: Yes

Subgroup Visit	Vutrisiran (HELIOS-A) (N=75)	Patisiran (HELIOS-A) (N=33)
Baseline		
n	75	33
Mean (SD)	22.06 (21.61)	22.20 (19.75)
SE	2.49	3.44
Median	12.50	17.50
Min, Max	0.0, 86.0	0.0, 66.9
Month 9		
Actual Value		
n	74	32
Mean (SD)	21.23 (21.35)	21.80 (21.70)
SE	2.48	3.84
Median	13.25	17.25
Min, Max	0.0, 89.1	0.0, 80.0
Change from baseline		
n	74	32
Mean (SD)	-0.69 (6.06)	-0.25 (12.13)
SE	0.70	2.14
Median	0.00	-0.69
Min, Max	-20.3, 17.0	-23.5, 46.4

mNIS+7 score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurologic impairment (range = 0 to 304). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 2.8
Modified Neuropathy Impairment Score +7 (mNIS+7) Components: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Component: Neuropathy Impairment Score - Weakness (NIS-W)

Previous Tetramer Stabilizer Use: Yes

Subgroup Visit	Vutrisiran (HELIOS-A) (N=75)	Patisiran (HELIOS-A) (N=33)
Month 18		
Actual Value		
n	71	29
Mean (SD)	23.90 (24.08)	23.50 (24.12)
SE	2.86	4.48
Median	14.50	16.00
Min, Max	0.0, 101.3	0.0, 97.4
Change from baseline		
n	71	29
Mean (SD)	2.25 (10.33)	2.09 (17.13)
SE	1.23	3.18
Median	1.50	0.00
Min, Max	-14.0, 59.5	-39.5, 74.1

mNIS+7 score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurologic impairment (range = 0 to 304). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 2.8
Modified Neuropathy Impairment Score +7 (mNIS+7) Components: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Component: Neuropathy Impairment Score - Weakness (NIS-W)

Previous Tetramer Stabilizer Use: No

Subgroup Visit	Vutrisiran (HELIOS-A) (N=47)	Patisiran (HELIOS-A) (N=9)
Baseline		
n	47	9
Mean (SD)	19.02 (16.23)	18.99 (15.23)
SE	2.37	5.08
Median	13.00	20.50
Min, Max	0.0, 53.9	2.0, 46.0
Month 9		
Actual Value		
n	43	8
Mean (SD)	17.82 (15.51)	14.58 (15.13)
SE	2.37	5.35
Median	14.00	8.25
Min, Max	0.0, 60.3	1.0, 46.5
Change from baseline		
n	43	8
Mean (SD)	0.64 (6.24)	-1.03 (6.23)
SE	0.95	2.20
Median	0.50	-0.31
Min, Max	-16.0, 15.9	-10.0, 10.5

mNIS+7 score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurologic impairment (range = 0 to 304). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 2.8
Modified Neuropathy Impairment Score +7 (mNIS+7) Components: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Component: Neuropathy Impairment Score - Weakness (NIS-W)

Previous Tetramer Stabilizer Use: No

Subgroup Visit	Vutrisiran (HELIOS-A) (N=47)	Patisiran (HELIOS-A) (N=9)
Month 18		
Actual Value		
n	44	7
Mean (SD)	19.54 (18.13)	11.95 (15.71)
SE	2.73	5.94
Median	10.81	4.00
Min, Max	0.0, 64.6	1.5, 43.3
Change from baseline		
n	44	7
Mean (SD)	0.78 (6.56)	-2.54 (7.34)
SE	0.99	2.78
Median	0.50	-0.50
Min, Max	-11.0, 18.0	-16.5, 7.3

mNIS+7 score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurologic impairment (range = 0 to 304). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 2.8
Modified Neuropathy Impairment Score +7 (mNIS+7) Components: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Component: Neuropathy Impairment Score - Weakness (NIS-W)

Genotype: V30M

Subgroup Visit	Vutrisiran (HELIOS-A) (N=54)	Patisiran (HELIOS-A) (N=20)
Baseline		
n	54	20
Mean (SD)	21.84 (19.66)	24.81 (19.92)
SE	2.67	4.45
Median	14.44	20.13
Min, Max	0.0, 66.9	1.0, 66.9
Month 9		
Actual Value		
n	52	20
Mean (SD)	21.17 (19.16)	22.24 (19.63)
SE	2.66	4.39
Median	18.44	17.69
Min, Max	0.0, 67.5	0.0, 80.0
Change from baseline		
n	52	20
Mean (SD)	-0.02 (4.85)	-2.57 (9.72)
SE	0.67	2.17
Median	0.00	-0.94
Min, Max	-12.5, 11.0	-23.5, 16.0

mNIS+7 score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurologic impairment (range = 0 to 304). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 2.8
Modified Neuropathy Impairment Score +7 (mNIS+7) Components: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Component: Neuropathy Impairment Score - Weakness (NIS-W)

Genotype: V30M

Subgroup Visit	Vutrisiran (HELIOS-A) (N=54)	Patisiran (HELIOS-A) (N=20)
Month 18		
Actual Value		
n	52	19
Mean (SD)	23.37 (20.36)	22.81 (17.74)
SE	2.82	4.07
Median	18.38	18.00
Min, Max	0.0, 73.4	0.0, 71.5
Change from baseline		
n	52	19
Mean (SD)	1.93 (6.28)	-0.88 (7.79)
SE	0.87	1.79
Median	1.50	-1.00
Min, Max	-13.6, 15.3	-20.9, 10.0

mNIS+7 score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurologic impairment (range = 0 to 304). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 2.8
Modified Neuropathy Impairment Score +7 (mNIS+7) Components: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Component: Neuropathy Impairment Score - Weakness (NIS-W)

Genotype: non-V30M

Subgroup Visit	Vutrisiran (HELIOS-A) (N=68)	Patisiran (HELIOS-A) (N=22)
Baseline		
n	68	22
Mean (SD)	20.14 (19.84)	18.52 (17.53)
SE	2.41	3.74
Median	12.25	13.75
Min, Max	0.0, 86.0	0.0, 52.4
Month 9		
Actual Value		
n	65	20
Mean (SD)	19.02 (19.70)	18.47 (21.85)
SE	2.44	4.89
Median	13.00	6.50
Min, Max	0.0, 89.1	0.0, 69.6
Change from baseline		
n	65	20
Mean (SD)	-0.34 (7.02)	1.76 (12.25)
SE	0.87	2.74
Median	0.13	0.00
Min, Max	-20.3, 17.0	-17.5, 46.4

mNIS+7 score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurologic impairment (range = 0 to 304). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 2.8
Modified Neuropathy Impairment Score +7 (mNIS+7) Components: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Component: Neuropathy Impairment Score - Weakness (NIS-W)

Genotype: non-V30M

Subgroup Visit	Vutrisiran (HELIOS-A) (N=68)	Patisiran (HELIOS-A) (N=22)
Month 18		
Actual Value		
n	63	17
Mean (SD)	21.29 (23.41)	19.52 (28.25)
SE	2.95	6.85
Median	10.63	4.00
Min, Max	0.0, 101.3	0.0, 97.4
Change from baseline		
n	63	17
Mean (SD)	1.49 (10.89)	3.51 (21.50)
SE	1.37	5.21
Median	0.00	0.00
Min, Max	-14.0, 59.5	-39.5, 74.1

mNIS+7 score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurologic impairment (range = 0 to 304). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 2.8
Modified Neuropathy Impairment Score +7 (mNIS+7) Components: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Component: Neuropathy Impairment Score - Weakness (NIS-W)

FAP Stage: I

Subgroup Visit	Vutrisiran (HELIOS-A) (N=84)	Patisiran (HELIOS-A) (N=31)
Baseline		
n	84	31
Mean (SD)	13.70 (15.22)	14.72 (15.48)
SE	1.66	2.78
Median	8.25	10.00
Min, Max	0.0, 66.9	0.0, 66.9
Month 9		
Actual Value		
n	82	30
Mean (SD)	12.96 (14.94)	13.92 (16.99)
SE	1.65	3.10
Median	6.56	9.75
Min, Max	0.0, 67.5	0.0, 69.6
Change from baseline		
n	82	30
Mean (SD)	-0.12 (5.16)	0.25 (11.12)
SE	0.57	2.03
Median	0.00	-0.50
Min, Max	-20.3, 11.5	-19.9, 46.4

mNIS+7 score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurologic impairment (range = 0 to 304). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 2.8
Modified Neuropathy Impairment Score +7 (mNIS+7) Components: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Component: Neuropathy Impairment Score - Weakness (NIS-W)

FAP Stage: I

Subgroup Visit	Vutrisiran (HELIOS-A) (N=84)	Patisiran (HELIOS-A) (N=31)
Month 18		
Actual Value		
n	81	29
Mean (SD)	14.92 (17.43)	14.55 (19.14)
SE	1.94	3.55
Median	7.00	10.50
Min, Max	0.0, 73.4	0.0, 97.4
Change from baseline		
n	81	29
Mean (SD)	1.52 (9.48)	0.66 (17.07)
SE	1.05	3.17
Median	1.00	-0.50
Min, Max	-14.0, 59.5	-39.5, 74.1

mNIS+7 score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurologic impairment (range = 0 to 304). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 2.8
Modified Neuropathy Impairment Score +7 (mNIS+7) Components: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Component: Neuropathy Impairment Score - Weakness (NIS-W)

FAP Stage: II&III

Subgroup Visit	Vutrisiran (HELIOS-A) (N=38)	Patisiran (HELIOS-A) (N=11)
Baseline		
n	38	11
Mean (SD)	36.77 (19.30)	40.66 (13.23)
SE	3.13	3.99
Median	37.94	41.13
Min, Max	6.0, 86.0	23.5, 66.1
Month 9		
Actual Value		
n	35	10
Mean (SD)	36.41 (18.89)	39.65 (18.86)
SE	3.19	5.96
Median	38.00	33.69
Min, Max	0.0, 89.1	18.9, 80.0
Change from baseline		
n	35	10
Mean (SD)	-0.38 (8.04)	-2.36 (11.54)
SE	1.36	3.65
Median	0.38	-3.13
Min, Max	-16.8, 17.0	-23.5, 13.9

mNIS+7 score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurologic impairment (range = 0 to 304). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 2.8
Modified Neuropathy Impairment Score +7 (mNIS+7) Components: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Component: Neuropathy Impairment Score - Weakness (NIS-W)

FAP Stage: II&III

Subgroup Visit	Vutrisiran (HELIOS-A) (N=38)	Patisiran (HELIOS-A) (N=11)
Month 18		
Actual Value		
n	34	7
Mean (SD)	39.65 (22.21)	49.05 (16.08)
SE	3.81	6.08
Median	36.38	43.25
Min, Max	4.0, 101.3	33.0, 71.5
Change from baseline		
n	34	7
Mean (SD)	2.11 (8.12)	3.39 (8.74)
SE	1.39	3.30
Median	1.75	5.38
Min, Max	-10.4, 24.1	-5.8, 19.0

mNIS+7 score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurologic impairment (range = 0 to 304). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 2.8
Modified Neuropathy Impairment Score +7 (mNIS+7) Components: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Component: Neuropathy Impairment Score - Weakness (NIS-W)

Cardiac Subpopulation: Yes

Subgroup Visit	Vutrisiran (HELIOS-A) (N=40)	Patisiran (HELIOS-A) (N=14)
Baseline		
n	40	14
Mean (SD)	28.12 (20.17)	26.46 (20.31)
SE	3.19	5.43
Median	31.25	25.75
Min, Max	0.0, 86.0	0.0, 66.1
Month 9		
Actual Value		
n	38	14
Mean (SD)	26.88 (21.06)	33.32 (24.88)
SE	3.42	6.65
Median	23.50	32.56
Min, Max	0.0, 89.1	0.0, 80.0
Change from baseline		
n	38	14
Mean (SD)	-0.90 (5.72)	6.87 (13.12)
SE	0.93	3.51
Median	0.00	3.00
Min, Max	-12.5, 7.5	-3.8, 46.4

mNIS+7 score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurologic impairment (range = 0 to 304). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 2.8
Modified Neuropathy Impairment Score +7 (mNIS+7) Components: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Component: Neuropathy Impairment Score - Weakness (NIS-W)

Cardiac Subpopulation: Yes

Subgroup Visit	Vutrisiran (HELIOS-A) (N=40)	Patisiran (HELIOS-A) (N=14)
Month 18		
Actual Value		
n	37	13
Mean (SD)	29.23 (22.88)	32.84 (30.45)
SE	3.76	8.45
Median	31.50	23.00
Min, Max	0.0, 101.3	0.0, 97.4
Change from baseline		
n	37	13
Mean (SD)	1.94 (12.05)	6.73 (24.41)
SE	1.98	6.77
Median	0.00	5.38
Min, Max	-13.6, 59.5	-39.5, 74.1

mNIS+7 score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurologic impairment (range = 0 to 304). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 2.8
Modified Neuropathy Impairment Score +7 (mNIS+7) Components: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Component: Neuropathy Impairment Score - Weakness (NIS-W)

Cardiac Subpopulation: No

Subgroup Visit	Vutrisiran (HELIOS-A) (N=82)	Patisiran (HELIOS-A) (N=28)
Baseline		
n	82	28
Mean (SD)	17.36 (18.58)	19.04 (17.78)
SE	2.05	3.36
Median	8.75	15.00
Min, Max	0.0, 72.9	0.0, 66.9
Month 9		
Actual Value		
n	79	26
Mean (SD)	16.65 (17.76)	13.37 (13.95)
SE	2.00	2.74
Median	10.00	10.56
Min, Max	0.0, 73.5	0.0, 47.0
Change from baseline		
n	79	26
Mean (SD)	0.14 (6.32)	-4.32 (7.64)
SE	0.71	1.50
Median	0.13	-1.00
Min, Max	-20.3, 17.0	-23.5, 7.0

mNIS+7 score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurologic impairment (range = 0 to 304). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 2.8
Modified Neuropathy Impairment Score +7 (mNIS+7) Components: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Component: Neuropathy Impairment Score - Weakness (NIS-W)

Cardiac Subpopulation: No

Subgroup Visit	Vutrisiran (HELIOS-A) (N=82)	Patisiran (HELIOS-A) (N=28)
Month 18		
Actual Value		
n	78	23
Mean (SD)	18.91 (20.92)	14.71 (14.57)
SE	2.37	3.04
Median	10.00	11.00
Min, Max	0.0, 82.4	0.0, 48.3
Change from baseline		
n	78	23
Mean (SD)	1.57 (7.34)	-1.94 (6.35)
SE	0.83	1.32
Median	1.06	-1.00
Min, Max	-14.0, 24.1	-20.9, 8.0

mNIS+7 score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurologic impairment (range = 0 to 304). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 2.8
Modified Neuropathy Impairment Score +7 (mNIS+7) Components: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Component: Neuropathy Impairment Score - Weakness (NIS-W)

Weight (kg): <65

Subgroup Visit	Vutrisiran (HELIOS-A) (N=46)	Patisiran (HELIOS-A) (N=15)
Baseline		
n	46	15
Mean (SD)	27.49 (19.74)	21.87 (19.96)
SE	2.91	5.15
Median	30.00	19.75
Min, Max	0.0, 86.0	0.0, 66.1
Month 9		
Actual Value		
n	44	15
Mean (SD)	26.88 (20.79)	22.83 (25.96)
SE	3.13	6.70
Median	28.19	17.00
Min, Max	1.0, 89.1	0.0, 80.0
Change from baseline		
n	44	15
Mean (SD)	-0.29 (6.66)	0.97 (14.50)
SE	1.00	3.74
Median	0.25	-1.00
Min, Max	-20.3, 17.0	-17.3, 46.4

mNIS+7 score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurologic impairment (range = 0 to 304). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

Alnylam Pharmaceuticals Inc.
ALN-TTRSC02-002

Table 2.8
Modified Neuropathy Impairment Score +7 (mNIS+7) Components: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Component: Neuropathy Impairment Score - Weakness (NIS-W)

Weight (kg): <65

Subgroup Visit	Vutrisiran (HELIOS-A) (N=46)	Patisiran (HELIOS-A) (N=15)
Month 18		
Actual Value		
n	42	13
Mean (SD)	28.36 (22.54)	22.88 (29.92)
SE	3.48	8.30
Median	31.56	11.00
Min, Max	0.0, 101.3	0.0, 97.4
Change from baseline		
n	42	13
Mean (SD)	1.75 (8.57)	1.77 (24.88)
SE	1.32	6.90
Median	0.75	-1.00
Min, Max	-13.9, 24.1	-39.5, 74.1

mNIS+7 score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurologic impairment (range = 0 to 304). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

Alnylam Pharmaceuticals Inc.
ALN-TTRSC02-002

Table 2.8
Modified Neuropathy Impairment Score +7 (mNIS+7) Components: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Component: Neuropathy Impairment Score - Weakness (NIS-W)

Weight (kg): ≥65

Subgroup Visit	Vutrisiran (HELIOS-A) (N=76)	Patisiran (HELIOS-A) (N=27)
Baseline		
n	76	27
Mean (SD)	16.90 (18.69)	21.31 (18.42)
SE	2.14	3.55
Median	8.75	17.50
Min, Max	0.0, 72.9	0.0, 66.9
Month 9		
Actual Value		
n	73	25
Mean (SD)	15.82 (17.39)	18.87 (17.03)
SE	2.03	3.41
Median	9.00	11.50
Min, Max	0.0, 73.5	0.0, 59.3
Change from baseline		
n	73	25
Mean (SD)	-0.14 (5.84)	-1.23 (8.78)
SE	0.68	1.76
Median	0.00	0.00
Min, Max	-16.8, 15.9	-23.5, 16.0

mNIS+7 score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurologic impairment (range = 0 to 304). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

Alnylam Pharmaceuticals Inc.
ALN-TTRSC02-002

Table 2.8
Modified Neuropathy Impairment Score +7 (mNIS+7) Components: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Component: Neuropathy Impairment Score - Weakness (NIS-W)

Weight (kg): ≥65

Subgroup Visit	Vutrisiran (HELIOS-A) (N=76)	Patisiran (HELIOS-A) (N=27)
Month 18		
Actual Value		
n	73	23
Mean (SD)	18.70 (21.05)	20.34 (18.75)
SE	2.46	3.91
Median	10.00	16.00
Min, Max	0.0, 82.4	0.0, 71.4
Change from baseline		
n	73	23
Mean (SD)	1.66 (9.40)	0.86 (7.47)
SE	1.10	1.56
Median	1.13	0.00
Min, Max	-14.0, 59.5	-20.9, 19.0

mNIS+7 score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurologic impairment (range = 0 to 304). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

mNIS+7 – Domäne NIS-*Reflexes*

Alnylam Pharmaceuticals Inc.
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Table 2.6
Modified Neuropathy Impairment Score +7 (mNIS+7) Component Scores: Change from Baseline to Month 18, MMRM Model
Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A) Subgroup Analysis
mITT Population

Neuropathy Impairment Score - Reflexes (NIS-R)

Subgroup Visit	LS Mean (95% CI) Vutrisiran (HELIOS-A) (N=122)	LS Mean (95% CI) Patisiran (HELIOS-A) (N=42)	LS Mean Difference (Vutrisiran-Patisiran) (95% CI), p-value	Standardized Effect Size (95% CI)
Age (years)				
<65	75	30		
Month 9	-0.34 (-1.00, 0.32)	-0.34 (-1.39, 0.71)	-0.00 (-1.24, 1.23), 0.9986	-0.00 (-0.42, 0.42)
Month 18	-0.00 (-0.71, 0.71)	0.68 (-0.49, 1.86)	-0.69 (-2.05, 0.68), 0.3233	-0.21 (-0.64, 0.22)
≥65	44	10		
Month 9	0.71 (-0.13, 1.54)	0.93 (-0.78, 2.65)	-0.23 (-2.14, 1.68), 0.8139	-0.07 (-0.75, 0.61)
Month 18	1.04 (0.16, 1.93)	1.96 (0.16, 3.76)	-0.91 (-2.92, 1.09), 0.3702	-0.26 (-0.98, 0.45)
p-value of Treatment*Age	0.8367			

mNIS+7 score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurologic impairment (range = 0 to 304). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.
LS estimates and p-value derived from mixed-effects model for repeated measures (MMRM), controlling for categorical factors (treatment, visit), the subgroup variable, continuous covariate (baseline value), and interaction (treatment by visit, treatment by subgroup).
Standardized effect size (d) = LS mean difference/estimated pooled standard deviation with the small sample bias correction.

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

Alnylam Pharmaceuticals Inc.
ALN-TTRSC02-002

Table 2.6
Modified Neuropathy Impairment Score +7 (mNIS+7) Component Scores: Change from Baseline to Month 18, MMRM Model
Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A) Subgroup Analysis
mITT Population

Neuropathy Impairment Score - Reflexes (NIS-R)

Subgroup Visit	LS Mean (95% CI) Vutrisiran (HELIOS-A) (N=122)	LS Mean (95% CI) Patisiran (HELIOS-A) (N=42)	LS Mean Difference (Vutrisiran-Patisiran) (95% CI), p-value	Standardized Effect Size (95% CI)
Sex				
Male	77	25		
Month 9	0.03 (-0.63, 0.69)	-0.34 (-1.49, 0.82)	0.37 (-0.96, 1.70), 0.5826	0.14 (-0.31, 0.59)
Month 18	0.37 (-0.34, 1.08)	0.69 (-0.57, 1.94)	-0.32 (-1.76, 1.12), 0.6644	-0.09 (-0.55, 0.38)
Female	42	15		
Month 9	0.06 (-0.80, 0.93)	0.53 (-0.92, 1.99)	-0.47 (-2.15, 1.22), 0.5844	-0.13 (-0.71, 0.45)
Month 18	0.40 (-0.50, 1.30)	1.55 (0.02, 3.09)	-1.16 (-2.93, 0.62), 0.2005	-0.42 (-1.02, 0.19)
p-value of Treatment*Sex	0.4154			

mNIS+7 score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurologic impairment (range = 0 to 304). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.
LS estimates and p-value derived from mixed-effects model for repeated measures (MMRM), controlling for categorical factors (treatment, visit), the subgroup variable, continuous covariate (baseline value), and interaction (treatment by visit, treatment by subgroup).
Standardized effect size (d) = LS mean difference/estimated pooled standard deviation with the small sample bias correction.

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

Alnylam Pharmaceuticals Inc.
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Table 2.6
Modified Neuropathy Impairment Score +7 (mNIS+7) Component Scores: Change from Baseline to Month 18, MMRM Model
Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A) Subgroup Analysis
mITT Population

Neuropathy Impairment Score - Reflexes (NIS-R)

Subgroup Visit	LS Mean (95% CI) Vutrisiran (HELIOS-A) (N=122)	LS Mean (95% CI) Patisiran (HELIOS-A) (N=42)	LS Mean Difference (Vutrisiran-Patisiran) (95% CI), p-value	Standardized Effect Size (95% CI)
Race				
White	84	28		
Month 9	-0.33 (-0.96, 0.29)	-0.23 (-1.30, 0.85)	-0.11 (-1.35, 1.14), 0.8645	-0.04 (-0.47, 0.38)
Month 18	0.00 (-0.68, 0.68)	0.79 (-0.40, 1.99)	-0.79 (-2.17, 0.58), 0.2567	-0.29 (-0.73, 0.15)
All Other Races	35	12		
Month 9	0.96 (0.03, 1.89)	0.46 (-1.12, 2.04)	0.50 (-1.34, 2.34), 0.5934	0.14 (-0.51, 0.78)
Month 18	1.30 (0.33, 2.26)	1.48 (-0.18, 3.15)	-0.19 (-2.12, 1.75), 0.8489	-0.04 (-0.71, 0.63)
p-value of Treatment*Race	0.5723			

mNIS+7 score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurologic impairment (range = 0 to 304). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.
LS estimates and p-value derived from mixed-effects model for repeated measures (MMRM), controlling for categorical factors (treatment, visit), the subgroup variable, continuous covariate (baseline value), and interaction (treatment by visit, treatment by subgroup).
Standardized effect size (d) = LS mean difference/estimated pooled standard deviation with the small sample bias correction.

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Table 2.6
Modified Neuropathy Impairment Score +7 (mNIS+7) Component Scores: Change from Baseline to Month 18, MMRM Model
Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A) Subgroup Analysis
mITT Population

Neuropathy Impairment Score - Reflexes (NIS-R)

Subgroup Visit	LS Mean (95% CI) Vutrisiran (HELIOS-A) (N=122)	LS Mean (95% CI) Patisiran (HELIOS-A) (N=42)	LS Mean Difference (Vutrisiran-Patisiran) (95% CI), p-value	Standardized Effect Size (95% CI)
Region				
North America	27	8		
Month 9	-0.65 (-1.74, 0.43)	-0.04 (-1.99, 1.91)	-0.61 (-2.83, 1.61), 0.5891	-0.21 (-0.99, 0.57)
Month 18	-0.32 (-1.43, 0.80)	0.99 (-1.07, 3.04)	-1.30 (-3.63, 1.03), 0.2711	-0.37 (-1.25, 0.50)
Western Europe	40	18		
Month 9	0.49 (-0.39, 1.36)	-0.45 (-1.77, 0.88)	0.94 (-0.65, 2.52), 0.2439	0.26 (-0.29, 0.82)
Month 18	0.82 (-0.09, 1.74)	0.58 (-0.82, 1.99)	0.24 (-1.43, 1.92), 0.7734	0.09 (-0.46, 0.64)
Rest of World	52	14		
Month 9	0.05 (-0.74, 0.84)	0.55 (-0.94, 2.03)	-0.50 (-2.17, 1.18), 0.5588	-0.19 (-0.78, 0.39)
Month 18	0.38 (-0.45, 1.22)	1.57 (0.00, 3.14)	-1.19 (-2.97, 0.59), 0.1879	-0.31 (-0.92, 0.29)
p-value of Treatment*Region	0.3397			

mNIS+7 score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurologic impairment (range = 0 to 304). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.
LS estimates and p-value derived from mixed-effects model for repeated measures (MMRM), controlling for categorical factors (treatment, visit), the subgroup variable, continuous covariate (baseline value), and interaction (treatment by visit, treatment by subgroup).
Standardized effect size (d) = LS mean difference/estimated pooled standard deviation with the small sample bias correction.

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Table 2.6
Modified Neuropathy Impairment Score +7 (mNIS+7) Component Scores: Change from Baseline to Month 18, MMRM Model
Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A) Subgroup Analysis
mITT Population

Neuropathy Impairment Score - Reflexes (NIS-R)

Subgroup Visit	LS Mean (95% CI) Vutrisiran (HELIOS-A) (N=122)	LS Mean (95% CI) Patisiran (HELIOS-A) (N=42)	LS Mean Difference (Vutrisiran-Patisiran) (95% CI), p-value	Standardized Effect Size (95% CI)
Baseline NIS				
<50	77	27		
Month 9	-0.37 (-1.03, 0.30)	-0.66 (-1.80, 0.47)	0.30 (-0.99, 1.58), 0.6499	0.09 (-0.34, 0.53)
Month 18	-0.04 (-0.76, 0.67)	0.35 (-0.89, 1.58)	-0.39 (-1.78, 1.00), 0.5797	-0.11 (-0.56, 0.34)
≥50	42	13		
Month 9	0.82 (-0.08, 1.73)	1.21 (-0.36, 2.77)	-0.38 (-2.13, 1.36), 0.6640	-0.14 (-0.76, 0.47)
Month 18	1.15 (0.22, 2.08)	2.22 (0.58, 3.85)	-1.07 (-2.89, 0.75), 0.2481	-0.40 (-1.04, 0.24)
p-value of Treatment*Baseline NIS	0.5132			

mNIS+7 score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurologic impairment (range = 0 to 304). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.
LS estimates and p-value derived from mixed-effects model for repeated measures (MMRM), controlling for categorical factors (treatment, visit), the subgroup variable, continuous covariate (baseline value), and interaction (treatment by visit, treatment by subgroup).
Standardized effect size (d) = LS mean difference/estimated pooled standard deviation with the small sample bias correction.

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

Alnylam Pharmaceuticals Inc.
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Table 2.6
Modified Neuropathy Impairment Score +7 (mNIS+7) Component Scores: Change from Baseline to Month 18, MMRM Model
Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A) Subgroup Analysis
mITT Population

Neuropathy Impairment Score - Reflexes (NIS-R)

Subgroup Visit	LS Mean (95% CI) Vutrisiran (HELIOS-A) (N=122)	LS Mean (95% CI) Patisiran (HELIOS-A) (N=42)	LS Mean Difference (Vutrisiran-Patisiran) (95% CI), p-value	Standardized Effect Size (95% CI)
Previous Tetramer Stabilizer Use				
Yes	74	32		
Month 9	-0.04 (-0.71, 0.63)	0.06 (-0.97, 1.10)	-0.11 (-1.34, 1.13), 0.8648	-0.04 (-0.45, 0.37)
Month 18	0.29 (-0.43, 1.01)	1.08 (-0.07, 2.24)	-0.80 (-2.16, 0.57), 0.2504	-0.24 (-0.67, 0.18)
No	45	8		
Month 9	0.19 (-0.65, 1.04)	-0.32 (-2.28, 1.64)	0.51 (-1.61, 2.64), 0.6339	0.15 (-0.59, 0.89)
Month 18	0.53 (-0.35, 1.40)	0.70 (-1.33, 2.73)	-0.18 (-2.38, 2.03), 0.8757	-0.05 (-0.84, 0.74)
p-value of Treatment*Previous Tetramer Stabilizer Use	0.6040			

mNIS+7 score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurologic impairment (range = 0 to 304). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.
LS estimates and p-value derived from mixed-effects model for repeated measures (MMRM), controlling for categorical factors (treatment, visit), the subgroup variable, continuous covariate (baseline value), and interaction (treatment by visit, treatment by subgroup).
Standardized effect size (d) = LS mean difference/estimated pooled standard deviation with the small sample bias correction.

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

Alnylam Pharmaceuticals Inc.
ALN-TTRSC02-002

Table 2.6
Modified Neuropathy Impairment Score +7 (mNIS+7) Component Scores: Change from Baseline to Month 18, MMRM Model
Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A) Subgroup Analysis
mITT Population

Neuropathy Impairment Score - Reflexes (NIS-R)

Subgroup Visit	LS Mean (95% CI) Vutrisiran (HELIOS-A) (N=122)	LS Mean (95% CI) Patisiran (HELIOS-A) (N=42)	LS Mean Difference (Vutrisiran-Patisiran) (95% CI), p-value	Standardized Effect Size (95% CI)
Genotype				
V30M	53	20		
Month 9	-0.38 (-1.16, 0.40)	0.05 (-1.21, 1.31)	-0.43 (-1.91, 1.04), 0.5639	-0.16 (-0.67, 0.35)
Month 18	-0.05 (-0.87, 0.78)	1.07 (-0.28, 2.42)	-1.11 (-2.69, 0.46), 0.1642	-0.42 (-0.94, 0.09)
non-V30M	66	20		
Month 9	0.39 (-0.32, 1.09)	-0.09 (-1.35, 1.17)	0.48 (-0.96, 1.92), 0.5138	0.15 (-0.35, 0.64)
Month 18	0.72 (-0.03, 1.48)	0.93 (-0.46, 2.31)	-0.20 (-1.78, 1.38), 0.7993	-0.05 (-0.58, 0.48)
p-value of Treatment*Genotype	0.3577			

mNIS+7 score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurologic impairment (range = 0 to 304). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.
LS estimates and p-value derived from mixed-effects model for repeated measures (MMRM), controlling for categorical factors (treatment, visit), the subgroup variable, continuous covariate (baseline value), and interaction (treatment by visit, treatment by subgroup).
Standardized effect size (d) = LS mean difference/estimated pooled standard deviation with the small sample bias correction.

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

Alnylam Pharmaceuticals Inc.
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Table 2.6
Modified Neuropathy Impairment Score +7 (mNIS+7) Component Scores: Change from Baseline to Month 18, MMRM Model
Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A) Subgroup Analysis
mITT Population

Neuropathy Impairment Score - Reflexes (NIS-R)

Subgroup Visit	LS Mean (95% CI) Vutrisiran (HELIOS-A) (N=122)	LS Mean (95% CI) Patisiran (HELIOS-A) (N=42)	LS Mean Difference (Vutrisiran-Patisiran) (95% CI), p-value	Standardized Effect Size (95% CI)
FAP Stage				
I	83	30		
Month 9	-0.29 (-0.94, 0.36)	-0.35 (-1.42, 0.72)	0.06 (-1.17, 1.29), 0.9284	0.02 (-0.40, 0.43)
Month 18	0.04 (-0.66, 0.74)	0.69 (-0.48, 1.86)	-0.65 (-1.99, 0.70), 0.3429	-0.20 (-0.62, 0.23)
II&III	36	10		
Month 9	0.82 (-0.16, 1.81)	0.87 (-0.89, 2.63)	-0.04 (-2.01, 1.92), 0.9662	-0.02 (-0.71, 0.67)
Month 18	1.16 (0.14, 2.17)	1.90 (0.05, 3.76)	-0.75 (-2.81, 1.32), 0.4779	-0.22 (-0.98, 0.53)
p-value of Treatment*FAP Stage	0.9303			

mNIS+7 score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurologic impairment (range = 0 to 304). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.
LS estimates and p-value derived from mixed-effects model for repeated measures (MMRM), controlling for categorical factors (treatment, visit), the subgroup variable, continuous covariate (baseline value), and interaction (treatment by visit, treatment by subgroup).
Standardized effect size (d) = LS mean difference/estimated pooled standard deviation with the small sample bias correction.

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

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Table 2.6
Modified Neuropathy Impairment Score +7 (mNIS+7) Component Scores: Change from Baseline to Month 18, MMRM Model
Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A) Subgroup Analysis
mITT Population

Neuropathy Impairment Score - Reflexes (NIS-R)

Subgroup Visit	LS Mean (95% CI) Vutrisiran (HELIOS-A) (N=122)	LS Mean (95% CI) Patisiran (HELIOS-A) (N=42)	LS Mean Difference (Vutrisiran-Patisiran) (95% CI), p-value	Standardized Effect Size (95% CI)
Cardiac Subpopulation				
Yes	38	14		
Month 9	0.21 (-0.73, 1.14)	0.48 (-1.01, 1.98)	-0.28 (-2.02, 1.46), 0.7542	-0.11 (-0.72, 0.49)
Month 18	0.54 (-0.43, 1.51)	1.51 (-0.08, 3.09)	-0.96 (-2.80, 0.87), 0.3013	-0.27 (-0.90, 0.35)
No	81	26		
Month 9	-0.03 (-0.69, 0.62)	-0.30 (-1.44, 0.85)	0.26 (-1.04, 1.56), 0.6921	0.08 (-0.36, 0.52)
Month 18	0.30 (-0.41, 1.01)	0.73 (-0.53, 1.98)	-0.42 (-1.85, 1.00), 0.5570	-0.13 (-0.58, 0.32)
p-value of Treatment*Cardiac Subpopulation	0.6062			

mNIS+7 score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurologic impairment (range = 0 to 304). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.
LS estimates and p-value derived from mixed-effects model for repeated measures (MMRM), controlling for categorical factors (treatment, visit), the subgroup variable, continuous covariate (baseline value), and interaction (treatment by visit, treatment by subgroup).
Standardized effect size (d) = LS mean difference/estimated pooled standard deviation with the small sample bias correction.

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Table 2.6
Modified Neuropathy Impairment Score +7 (mNIS+7) Component Scores: Change from Baseline to Month 18, MMRM Model
Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A) Subgroup Analysis
mITT Population

Neuropathy Impairment Score - Reflexes (NIS-R)

Subgroup Visit	LS Mean (95% CI) Vutrisiran (HELIOS-A) (N=122)	LS Mean (95% CI) Patisiran (HELIOS-A) (N=42)	LS Mean Difference (Vutrisiran-Patisiran) (95% CI), p-value	Standardized Effect Size (95% CI)
Weight (kg)				
<65	44	15		
Month 9	-0.02 (-0.86, 0.82)	-0.74 (-2.19, 0.71)	0.72 (-0.97, 2.40), 0.4032	0.26 (-0.32, 0.84)
Month 18	0.31 (-0.58, 1.20)	0.28 (-1.26, 1.82)	0.03 (-1.76, 1.81), 0.9774	0.01 (-0.59, 0.60)
≥65	75	25		
Month 9	0.09 (-0.58, 0.75)	0.42 (-0.73, 1.56)	-0.33 (-1.66, 1.00), 0.6238	-0.10 (-0.55, 0.35)
Month 18	0.42 (-0.30, 1.14)	1.44 (0.18, 2.70)	-1.02 (-2.47, 0.43), 0.1662	-0.32 (-0.78, 0.15)
p-value of Treatment*Weight	0.3138			

mNIS+7 score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurologic impairment (range = 0 to 304). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.
LS estimates and p-value derived from mixed-effects model for repeated measures (MMRM), controlling for categorical factors (treatment, visit), the subgroup variable, continuous covariate (baseline value), and interaction (treatment by visit, treatment by subgroup).
Standardized effect size (d) = LS mean difference/estimated pooled standard deviation with the small sample bias correction.

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Table 2.8
Modified Neuropathy Impairment Score +7 (mNIS+7) Components: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Component: Neuropathy Impairment Score - Reflexes (NIS-R)

Age (years): <65

Subgroup Visit	Vutrisiran (HELIOS-A) (N=76)	Patisiran (HELIOS-A) (N=31)
Baseline		
n	76	31
Mean (SD)	9.48 (6.12)	9.48 (7.12)
SE	0.70	1.28
Median	8.25	7.00
Min, Max	0.0, 20.0	0.0, 20.0
Month 9		
Actual Value		
n	74	30
Mean (SD)	9.20 (6.13)	8.85 (6.97)
SE	0.71	1.27
Median	8.00	6.00
Min, Max	0.0, 20.0	0.0, 20.0
Change from baseline		
n	74	30
Mean (SD)	-0.26 (2.94)	-0.28 (2.79)
SE	0.34	0.51
Median	0.00	0.00
Min, Max	-13.0, 8.0	-8.0, 6.5

mNIS+7 score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurologic impairment (range = 0 to 304). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 2.8
Modified Neuropathy Impairment Score +7 (mNIS+7) Components: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Component: Neuropathy Impairment Score - Reflexes (NIS-R)

Age (years): <65

Subgroup Visit	Vutrisiran (HELIOS-A) (N=76)	Patisiran (HELIOS-A) (N=31)
Month 18		
Actual Value		
n	74	28
Mean (SD)	9.48 (5.90)	9.58 (6.87)
SE	0.69	1.30
Median	9.00	7.50
Min, Max	0.0, 20.0	0.0, 20.0
Change from baseline		
n	74	28
Mean (SD)	0.16 (3.62)	1.01 (2.83)
SE	0.42	0.53
Median	0.00	1.00
Min, Max	-13.5, 7.5	-6.0, 8.5

mNIS+7 score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurologic impairment (range = 0 to 304). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 2.8
Modified Neuropathy Impairment Score +7 (mNIS+7) Components: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Component: Neuropathy Impairment Score - Reflexes (NIS-R)

Age (years): ≥65

Subgroup Visit	Vutrisiran (HELIOS-A) (N=46)	Patisiran (HELIOS-A) (N=11)
Baseline		
n	46	11
Mean (SD)	11.76 (6.95)	11.18 (6.75)
SE	1.02	2.03
Median	13.50	10.00
Min, Max	0.0, 20.0	2.5, 20.0
Month 9		
Actual Value		
n	43	10
Mean (SD)	12.05 (6.36)	11.55 (6.14)
SE	0.97	1.94
Median	13.00	9.25
Min, Max	0.0, 20.0	3.5, 20.0
Change from baseline		
n	43	10
Mean (SD)	0.51 (3.66)	1.25 (2.97)
SE	0.56	0.94
Median	0.00	0.50
Min, Max	-6.0, 18.0	-3.0, 8.0

mNIS+7 score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurologic impairment (range = 0 to 304). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 2.8
Modified Neuropathy Impairment Score +7 (mNIS+7) Components: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Component: Neuropathy Impairment Score - Reflexes (NIS-R)

Age (years): ≥65

Subgroup Visit	Vutrisiran (HELIOS-A) (N=46)	Patisiran (HELIOS-A) (N=11)
Month 18		
Actual Value		
n	41	9
Mean (SD)	12.13 (6.81)	12.00 (7.28)
SE	1.06	2.43
Median	14.00	10.00
Min, Max	0.0, 20.0	3.0, 20.0
Change from baseline		
n	41	9
Mean (SD)	0.79 (3.56)	1.44 (3.88)
SE	0.56	1.29
Median	0.00	0.00
Min, Max	-8.0, 11.0	-3.5, 7.5

mNIS+7 score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurologic impairment (range = 0 to 304). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 2.8
Modified Neuropathy Impairment Score +7 (mNIS+7) Components: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Component: Neuropathy Impairment Score - Reflexes (NIS-R)

Sex: Male

Subgroup Visit	Vutrisiran (HELIOS-A) (N=79)	Patisiran (HELIOS-A) (N=27)
Baseline		
n	79	27
Mean (SD)	10.94 (6.49)	11.39 (7.03)
SE	0.73	1.35
Median	11.50	10.00
Min, Max	0.0, 20.0	0.5, 20.0
Month 9		
Actual Value		
n	76	25
Mean (SD)	10.83 (6.34)	10.48 (7.01)
SE	0.73	1.40
Median	10.75	8.00
Min, Max	0.0, 20.0	1.0, 20.0
Change from baseline		
n	76	25
Mean (SD)	-0.03 (2.75)	-0.22 (2.89)
SE	0.32	0.58
Median	0.00	0.00
Min, Max	-13.0, 8.0	-8.0, 8.0

mNIS+7 score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurologic impairment (range = 0 to 304). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 2.8
Modified Neuropathy Impairment Score +7 (mNIS+7) Components: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Component: Neuropathy Impairment Score - Reflexes (NIS-R)

Sex: Male

Subgroup Visit	Vutrisiran (HELIOS-A) (N=79)	Patisiran (HELIOS-A) (N=27)
Month 18		
Actual Value		
n	74	23
Mean (SD)	10.85 (6.23)	10.79 (7.07)
SE	0.72	1.47
Median	11.00	8.00
Min, Max	0.0, 20.0	2.0, 20.0
Change from baseline		
n	74	23
Mean (SD)	0.26 (4.06)	0.33 (2.80)
SE	0.47	0.58
Median	0.00	0.00
Min, Max	-13.5, 11.0	-6.0, 7.5

mNIS+7 score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurologic impairment (range = 0 to 304). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 2.8
Modified Neuropathy Impairment Score +7 (mNIS+7) Components: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Component: Neuropathy Impairment Score - Reflexes (NIS-R)

Sex: Female

Subgroup Visit	Vutrisiran (HELIOS-A) (N=43)	Patisiran (HELIOS-A) (N=15)
Baseline		
n	43	15
Mean (SD)	9.23 (6.47)	7.30 (6.26)
SE	0.99	1.62
Median	8.00	4.50
Min, Max	0.0, 20.0	0.0, 20.0
Month 9		
Actual Value		
n	41	15
Mean (SD)	9.17 (6.28)	7.93 (6.34)
SE	0.98	1.64
Median	7.00	6.00
Min, Max	0.0, 20.0	0.0, 20.0
Change from baseline		
n	41	15
Mean (SD)	0.13 (4.00)	0.63 (2.88)
SE	0.63	0.74
Median	0.00	1.00
Min, Max	-9.0, 18.0	-4.5, 6.5

mNIS+7 score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurologic impairment (range = 0 to 304). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 2.8
Modified Neuropathy Impairment Score +7 (mNIS+7) Components: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Component: Neuropathy Impairment Score - Reflexes (NIS-R)

Sex: Female

Subgroup Visit	Vutrisiran (HELIOS-A) (N=43)	Patisiran (HELIOS-A) (N=15)
Month 18		
Actual Value		
n	41	14
Mean (SD)	9.66 (6.54)	9.15 (6.89)
SE	1.02	1.84
Median	9.00	8.50
Min, Max	0.0, 20.0	0.0, 20.0
Change from baseline		
n	41	14
Mean (SD)	0.60 (2.60)	2.40 (3.14)
SE	0.41	0.84
Median	0.00	1.81
Min, Max	-5.0, 9.0	-2.0, 8.5

mNIS+7 score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurologic impairment (range = 0 to 304). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 2.8
Modified Neuropathy Impairment Score +7 (mNIS+7) Components: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Component: Neuropathy Impairment Score - Reflexes (NIS-R)

Race: White

Subgroup Visit	Vutrisiran (HELIOS-A) (N=86)	Patisiran (HELIOS-A) (N=29)
Baseline		
n	86	29
Mean (SD)	9.79 (6.49)	10.41 (7.13)
SE	0.70	1.32
Median	8.50	10.00
Min, Max	0.0, 20.0	0.0, 20.0
Month 9		
Actual Value		
n	83	28
Mean (SD)	9.31 (6.34)	9.86 (6.98)
SE	0.70	1.32
Median	8.00	7.00
Min, Max	0.0, 20.0	0.0, 20.0
Change from baseline		
n	83	28
Mean (SD)	-0.30 (2.67)	-0.21 (2.87)
SE	0.29	0.54
Median	0.00	0.00
Min, Max	-13.0, 4.0	-8.0, 8.0

mNIS+7 score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurologic impairment (range = 0 to 304). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 2.8
Modified Neuropathy Impairment Score +7 (mNIS+7) Components: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Component: Neuropathy Impairment Score - Reflexes (NIS-R)

Race: White

Subgroup Visit	Vutrisiran (HELIOS-A) (N=86)	Patisiran (HELIOS-A) (N=29)
Month 18		
Actual Value		
n	82	26
Mean (SD)	9.66 (6.27)	10.35 (7.12)
SE	0.69	1.40
Median	8.00	7.50
Min, Max	0.0, 20.0	0.0, 20.0
Change from baseline		
n	82	26
Mean (SD)	0.14 (2.68)	0.82 (3.13)
SE	0.30	0.61
Median	0.00	0.00
Min, Max	-11.5, 8.0	-6.0, 8.0

mNIS+7 score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurologic impairment (range = 0 to 304). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 2.8
Modified Neuropathy Impairment Score +7 (mNIS+7) Components: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Component: Neuropathy Impairment Score - Reflexes (NIS-R)

Race: All Other Races

Subgroup Visit	Vutrisiran (HELIOS-A) (N=36)	Patisiran (HELIOS-A) (N=13)
Baseline		
n	36	13
Mean (SD)	11.65 (6.47)	8.85 (6.79)
SE	1.08	1.88
Median	12.25	7.00
Min, Max	0.0, 20.0	0.5, 20.0
Month 9		
Actual Value		
n	34	12
Mean (SD)	12.54 (5.82)	8.75 (6.58)
SE	1.00	1.90
Median	13.25	7.25
Min, Max	0.0, 20.0	1.0, 20.0
Change from baseline		
n	34	12
Mean (SD)	0.81 (4.24)	0.83 (2.89)
SE	0.73	0.83
Median	0.00	0.25
Min, Max	-6.0, 18.0	-3.0, 6.5

mNIS+7 score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurologic impairment (range = 0 to 304). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 2.8
Modified Neuropathy Impairment Score +7 (mNIS+7) Components: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Component: Neuropathy Impairment Score - Reflexes (NIS-R)

Race: All Other Races

Subgroup Visit	Vutrisiran (HELIOS-A) (N=36)	Patisiran (HELIOS-A) (N=13)
Month 18		
Actual Value		
n	33	11
Mean (SD)	12.32 (6.19)	9.73 (6.85)
SE	1.08	2.07
Median	12.00	8.00
Min, Max	0.0, 20.0	2.0, 20.0
Change from baseline		
n	33	11
Mean (SD)	0.98 (5.24)	1.82 (2.93)
SE	0.91	0.88
Median	1.00	1.50
Min, Max	-13.5, 11.0	-3.0, 8.5

mNIS+7 score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurologic impairment (range = 0 to 304). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 2.8
Modified Neuropathy Impairment Score +7 (mNIS+7) Components: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Component: Neuropathy Impairment Score - Reflexes (NIS-R)

Region: North America

Subgroup Visit	Vutrisiran (HELIOS-A) (N=27)	Patisiran (HELIOS-A) (N=8)
Baseline		
n	27	8
Mean (SD)	7.57 (6.21)	9.13 (6.69)
SE	1.20	2.36
Median	7.00	7.50
Min, Max	0.0, 20.0	0.0, 20.0
Month 9		
Actual Value		
n	25	8
Mean (SD)	6.36 (5.49)	9.63 (6.48)
SE	1.10	2.29
Median	6.00	8.50
Min, Max	0.0, 20.0	0.0, 20.0
Change from baseline		
n	25	8
Mean (SD)	-0.78 (3.36)	0.50 (1.77)
SE	0.67	0.63
Median	0.00	0.50
Min, Max	-13.0, 3.0	-3.0, 3.0

mNIS+7 score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurologic impairment (range = 0 to 304). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 2.8
Modified Neuropathy Impairment Score +7 (mNIS+7) Components: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Component: Neuropathy Impairment Score - Reflexes (NIS-R)

Region: North America

Subgroup Visit	Vutrisiran (HELIOS-A) (N=27)	Patisiran (HELIOS-A) (N=8)
Month 18		
Actual Value		
n	25	6
Mean (SD)	7.84 (6.53)	8.67 (7.23)
SE	1.31	2.95
Median	6.00	7.00
Min, Max	0.0, 20.0	0.0, 20.0
Change from baseline		
n	25	6
Mean (SD)	0.74 (3.07)	0.33 (4.84)
SE	0.61	1.98
Median	0.00	0.00
Min, Max	-4.0, 11.0	-6.0, 8.0

mNIS+7 score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurologic impairment (range = 0 to 304). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 2.8
Modified Neuropathy Impairment Score +7 (mNIS+7) Components: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Component: Neuropathy Impairment Score - Reflexes (NIS-R)

Region: Western Europe

Subgroup Visit	Vutrisiran (HELIOS-A) (N=42)	Patisiran (HELIOS-A) (N=20)
Baseline		
n	42	20
Mean (SD)	9.44 (6.22)	9.65 (6.89)
SE	0.96	1.54
Median	8.50	8.75
Min, Max	0.0, 20.0	1.0, 20.0
Month 9		
Actual Value		
n	40	18
Mean (SD)	9.80 (6.29)	8.42 (6.45)
SE	0.99	1.52
Median	8.00	6.00
Min, Max	0.0, 20.0	0.0, 20.0
Change from baseline		
n	40	18
Mean (SD)	0.61 (3.65)	-0.08 (3.64)
SE	0.58	0.86
Median	0.00	0.00
Min, Max	-5.5, 18.0	-8.0, 8.0

mNIS+7 score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurologic impairment (range = 0 to 304). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 2.8
Modified Neuropathy Impairment Score +7 (mNIS+7) Components: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Component: Neuropathy Impairment Score - Reflexes (NIS-R)

Region: Western Europe

Subgroup Visit	Vutrisiran (HELIOS-A) (N=42)	Patisiran (HELIOS-A) (N=20)
Month 18		
Actual Value		
n	40	18
Mean (SD)	10.21 (6.02)	9.18 (6.52)
SE	0.95	1.54
Median	8.50	7.00
Min, Max	2.0, 20.0	2.0, 20.0
Change from baseline		
n	40	18
Mean (SD)	1.03 (2.77)	0.68 (2.86)
SE	0.44	0.67
Median	0.25	0.00
Min, Max	-4.5, 9.0	-4.0, 7.5

mNIS+7 score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurologic impairment (range = 0 to 304). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 2.8
Modified Neuropathy Impairment Score +7 (mNIS+7) Components: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Component: Neuropathy Impairment Score - Reflexes (NIS-R)

Region: Rest of World

Subgroup Visit	Vutrisiran (HELIOS-A) (N=53)	Patisiran (HELIOS-A) (N=14)
Baseline		
n	53	14
Mean (SD)	12.46 (6.30)	10.79 (7.67)
SE	0.87	2.05
Median	13.50	10.75
Min, Max	0.0, 20.0	0.5, 20.0
Month 9		
Actual Value		
n	52	14
Mean (SD)	12.46 (5.87)	10.89 (7.60)
SE	0.81	2.03
Median	12.75	10.00
Min, Max	0.0, 20.0	1.0, 20.0
Change from baseline		
n	52	14
Mean (SD)	-0.04 (2.75)	0.11 (2.39)
SE	0.38	0.64
Median	0.00	0.25
Min, Max	-9.0, 8.0	-3.5, 4.5

mNIS+7 score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurologic impairment (range = 0 to 304). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 2.8
Modified Neuropathy Impairment Score +7 (mNIS+7) Components: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Component: Neuropathy Impairment Score - Reflexes (NIS-R)

Region: Rest of World

Subgroup Visit	Vutrisiran (HELIOS-A) (N=53)	Patisiran (HELIOS-A) (N=14)
Month 18		
Actual Value		
n	50	13
Mean (SD)	11.89 (6.18)	12.23 (7.47)
SE	0.87	2.07
Median	12.00	10.00
Min, Max	0.0, 20.0	2.0, 20.0
Change from baseline		
n	50	13
Mean (SD)	-0.31 (4.30)	2.08 (2.29)
SE	0.61	0.64
Median	0.00	1.50
Min, Max	-13.5, 7.5	0.0, 8.5

mNIS+7 score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurologic impairment (range = 0 to 304). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

Alnylam Pharmaceuticals Inc.
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Table 2.8
Modified Neuropathy Impairment Score +7 (mNIS+7) Components: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Component: Neuropathy Impairment Score - Reflexes (NIS-R)

Baseline NIS: <50

Subgroup Visit	Vutrisiran (HELIOS-A) (N=78)	Patisiran (HELIOS-A) (N=27)
Baseline		
n	78	27
Mean (SD)	8.12 (6.02)	6.44 (5.16)
SE	0.68	0.99
Median	7.00	4.00
Min, Max	0.0, 20.0	0.0, 20.0
Month 9		
Actual Value		
n	77	27
Mean (SD)	8.16 (5.81)	6.63 (4.78)
SE	0.66	0.92
Median	6.00	6.00
Min, Max	0.0, 20.0	0.0, 20.0
Change from baseline		
n	77	27
Mean (SD)	0.06 (3.62)	0.19 (2.64)
SE	0.41	0.51
Median	0.00	0.00
Min, Max	-13.0, 18.0	-4.5, 8.0

mNIS+7 score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurologic impairment (range = 0 to 304). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

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Table 2.8
Modified Neuropathy Impairment Score +7 (mNIS+7) Components: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Component: Neuropathy Impairment Score - Reflexes (NIS-R)

Baseline NIS: <50

Subgroup Visit	Vutrisiran (HELIOS-A) (N=78)	Patisiran (HELIOS-A) (N=27)
Month 18		
Actual Value		
n	75	25
Mean (SD)	8.29 (5.92)	6.94 (5.11)
SE	0.68	1.02
Median	6.50	6.50
Min, Max	0.0, 20.0	0.0, 20.0
Change from baseline		
n	75	25
Mean (SD)	0.34 (3.84)	0.90 (3.49)
SE	0.44	0.70
Median	0.00	0.00
Min, Max	-13.5, 11.0	-6.0, 8.5

mNIS+7 score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurologic impairment (range = 0 to 304). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

Alnylam Pharmaceuticals Inc.
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Table 2.8
Modified Neuropathy Impairment Score +7 (mNIS+7) Components: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Component: Neuropathy Impairment Score - Reflexes (NIS-R)

Baseline NIS: ≥50

Subgroup Visit	Vutrisiran (HELIOS-A) (N=44)	Patisiran (HELIOS-A) (N=15)
Baseline		
n	44	15
Mean (SD)	14.27 (5.45)	16.20 (5.26)
SE	0.82	1.36
Median	16.25	19.00
Min, Max	2.0, 20.0	4.0, 20.0
Month 9		
Actual Value		
n	40	13
Mean (SD)	14.28 (5.34)	15.54 (6.52)
SE	0.85	1.81
Median	16.25	18.50
Min, Max	4.0, 20.0	2.0, 20.0
Change from baseline		
n	40	13
Mean (SD)	-0.05 (2.33)	-0.08 (3.45)
SE	0.37	0.96
Median	0.00	0.00
Min, Max	-6.0, 5.5	-8.0, 6.5

mNIS+7 score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurologic impairment (range = 0 to 304). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 2.8
Modified Neuropathy Impairment Score +7 (mNIS+7) Components: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Component: Neuropathy Impairment Score - Reflexes (NIS-R)

Baseline NIS: ≥50

Subgroup Visit	Vutrisiran (HELIOS-A) (N=44)	Patisiran (HELIOS-A) (N=15)
Month 18		
Actual Value		
n	40	12
Mean (SD)	14.44 (5.06)	16.88 (5.33)
SE	0.80	1.54
Median	16.00	19.75
Min, Max	4.0, 20.0	4.0, 20.0
Change from baseline		
n	40	12
Mean (SD)	0.46 (3.14)	1.55 (1.95)
SE	0.50	0.56
Median	0.00	1.00
Min, Max	-8.0, 7.0	0.0, 6.0

mNIS+7 score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurologic impairment (range = 0 to 304). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 2.8
Modified Neuropathy Impairment Score +7 (mNIS+7) Components: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Component: Neuropathy Impairment Score - Reflexes (NIS-R)

Previous Tetramer Stabilizer Use: Yes

Subgroup Visit	Vutrisiran (HELIOS-A) (N=75)	Patisiran (HELIOS-A) (N=33)
Baseline		
n	75	33
Mean (SD)	10.83 (6.25)	10.35 (6.78)
SE	0.72	1.18
Median	11.00	10.00
Min, Max	0.0, 20.0	1.0, 20.0
Month 9		
Actual Value		
n	74	32
Mean (SD)	10.66 (6.28)	10.03 (6.93)
SE	0.73	1.22
Median	10.00	7.00
Min, Max	0.0, 20.0	0.0, 20.0
Change from baseline		
n	74	32
Mean (SD)	-0.18 (2.80)	-0.02 (3.07)
SE	0.33	0.54
Median	0.00	0.00
Min, Max	-13.0, 5.5	-8.0, 8.0

mNIS+7 score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurologic impairment (range = 0 to 304). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 2.8
Modified Neuropathy Impairment Score +7 (mNIS+7) Components: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Component: Neuropathy Impairment Score - Reflexes (NIS-R)

Previous Tetramer Stabilizer Use: Yes

Subgroup Visit	Vutrisiran (HELIOS-A) (N=75)	Patisiran (HELIOS-A) (N=33)
Month 18		
Actual Value		
n	71	30
Mean (SD)	10.87 (6.20)	10.84 (6.96)
SE	0.74	1.27
Median	11.00	9.00
Min, Max	0.0, 20.0	2.0, 20.0
Change from baseline		
n	71	30
Mean (SD)	0.30 (3.63)	1.26 (2.70)
SE	0.43	0.49
Median	0.00	1.00
Min, Max	-13.5, 8.0	-4.0, 8.0

mNIS+7 score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurologic impairment (range = 0 to 304). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 2.8
Modified Neuropathy Impairment Score +7 (mNIS+7) Components: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Component: Neuropathy Impairment Score - Reflexes (NIS-R)

Previous Tetramer Stabilizer Use: No

Subgroup Visit	Vutrisiran (HELIOS-A) (N=47)	Patisiran (HELIOS-A) (N=9)
Baseline		
n	47	9
Mean (SD)	9.56 (6.90)	8.39 (7.89)
SE	1.01	2.63
Median	8.00	7.00
Min, Max	0.0, 20.0	0.0, 20.0
Month 9		
Actual Value		
n	43	8
Mean (SD)	9.55 (6.46)	7.50 (6.23)
SE	0.98	2.20
Median	8.00	7.00
Min, Max	0.0, 20.0	0.0, 20.0
Change from baseline		
n	43	8
Mean (SD)	0.38 (3.86)	0.56 (2.08)
SE	0.59	0.73
Median	0.00	0.25
Min, Max	-6.0, 18.0	-3.0, 4.5

mNIS+7 score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurologic impairment (range = 0 to 304). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 2.8
Modified Neuropathy Impairment Score +7 (mNIS+7) Components: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Component: Neuropathy Impairment Score - Reflexes (NIS-R)

Previous Tetramer Stabilizer Use: No

Subgroup Visit	Vutrisiran (HELIOS-A) (N=47)	Patisiran (HELIOS-A) (N=9)
Month 18		
Actual Value		
n	44	7
Mean (SD)	9.72 (6.56)	7.29 (6.60)
SE	0.99	2.49
Median	8.50	7.00
Min, Max	0.0, 20.0	0.0, 20.0
Change from baseline		
n	44	7
Mean (SD)	0.51 (3.58)	0.50 (4.55)
SE	0.54	1.72
Median	0.00	0.00
Min, Max	-8.0, 11.0	-6.0, 8.5

mNIS+7 score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurologic impairment (range = 0 to 304). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 2.8
Modified Neuropathy Impairment Score +7 (mNIS+7) Components: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Component: Neuropathy Impairment Score - Reflexes (NIS-R)

Genotype: V30M

Subgroup Visit	Vutrisiran (HELIOS-A) (N=54)	Patisiran (HELIOS-A) (N=20)
Baseline		
n	54	20
Mean (SD)	8.71 (5.99)	8.25 (6.29)
SE	0.82	1.41
Median	8.00	4.75
Min, Max	0.0, 20.0	0.0, 20.0
Month 9		
Actual Value		
n	52	20
Mean (SD)	8.34 (5.84)	8.70 (6.62)
SE	0.81	1.48
Median	7.00	6.00
Min, Max	0.0, 20.0	0.0, 20.0
Change from baseline		
n	52	20
Mean (SD)	-0.33 (2.41)	0.45 (3.50)
SE	0.33	0.78
Median	0.00	0.00
Min, Max	-9.0, 4.0	-8.0, 8.0

mNIS+7 score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurologic impairment (range = 0 to 304). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 2.8
Modified Neuropathy Impairment Score +7 (mNIS+7) Components: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Component: Neuropathy Impairment Score - Reflexes (NIS-R)

Genotype: V30M

Subgroup Visit	Vutrisiran (HELIOS-A) (N=54)	Patisiran (HELIOS-A) (N=20)
Month 18		
Actual Value		
n	52	20
Mean (SD)	8.91 (5.71)	9.46 (6.66)
SE	0.79	1.49
Median	7.75	7.00
Min, Max	0.0, 20.0	0.0, 20.0
Change from baseline		
n	52	20
Mean (SD)	0.44 (2.69)	1.21 (2.61)
SE	0.37	0.58
Median	0.00	0.00
Min, Max	-8.0, 6.5	-4.0, 7.5

mNIS+7 score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurologic impairment (range = 0 to 304). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 2.8
Modified Neuropathy Impairment Score +7 (mNIS+7) Components: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Component: Neuropathy Impairment Score - Reflexes (NIS-R)

Genotype: non-V30M

Subgroup Visit	Vutrisiran (HELIOS-A) (N=68)	Patisiran (HELIOS-A) (N=22)
Baseline		
n	68	22
Mean (SD)	11.63 (6.66)	11.45 (7.36)
SE	0.81	1.57
Median	12.25	12.00
Min, Max	0.0, 20.0	0.5, 20.0
Month 9		
Actual Value		
n	65	20
Mean (SD)	11.78 (6.35)	10.35 (7.04)
SE	0.79	1.57
Median	12.00	8.50
Min, Max	0.0, 20.0	0.0, 20.0
Change from baseline		
n	65	20
Mean (SD)	0.31 (3.75)	-0.25 (2.12)
SE	0.46	0.48
Median	0.00	0.00
Min, Max	-13.0, 18.0	-3.5, 4.5

mNIS+7 score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurologic impairment (range = 0 to 304). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 2.8
Modified Neuropathy Impairment Score +7 (mNIS+7) Components: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Component: Neuropathy Impairment Score - Reflexes (NIS-R)

Genotype: non-V30M

Subgroup Visit	Vutrisiran (HELIOS-A) (N=68)	Patisiran (HELIOS-A) (N=22)
Month 18		
Actual Value		
n	63	17
Mean (SD)	11.67 (6.60)	11.00 (7.39)
SE	0.83	1.79
Median	12.00	8.00
Min, Max	0.0, 20.0	2.0, 20.0
Change from baseline		
n	63	17
Mean (SD)	0.33 (4.23)	1.00 (3.61)
SE	0.53	0.87
Median	0.00	1.00
Min, Max	-13.5, 11.0	-6.0, 8.5

mNIS+7 score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurologic impairment (range = 0 to 304). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 2.8
Modified Neuropathy Impairment Score +7 (mNIS+7) Components: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Component: Neuropathy Impairment Score - Reflexes (NIS-R)

FAP Stage: I

Subgroup Visit	Vutrisiran (HELIOS-A) (N=84)	Patisiran (HELIOS-A) (N=31)
Baseline		
n	84	31
Mean (SD)	8.21 (5.90)	8.21 (6.65)
SE	0.64	1.19
Median	7.75	4.50
Min, Max	0.0, 20.0	0.0, 20.0
Month 9		
Actual Value		
n	82	30
Mean (SD)	8.24 (5.77)	7.90 (6.19)
SE	0.64	1.13
Median	6.50	6.00
Min, Max	0.0, 20.0	0.0, 20.0
Change from baseline		
n	82	30
Mean (SD)	0.08 (3.59)	0.08 (2.71)
SE	0.40	0.49
Median	0.00	0.00
Min, Max	-13.0, 18.0	-4.5, 8.0

mNIS+7 score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurologic impairment (range = 0 to 304). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 2.8
Modified Neuropathy Impairment Score +7 (mNIS+7) Components: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Component: Neuropathy Impairment Score - Reflexes (NIS-R)

FAP Stage: I

Subgroup Visit	Vutrisiran (HELIOS-A) (N=84)	Patisiran (HELIOS-A) (N=31)
Month 18		
Actual Value		
n	81	29
Mean (SD)	8.35 (5.71)	8.68 (6.47)
SE	0.63	1.20
Median	7.50	7.00
Min, Max	0.0, 20.0	0.0, 20.0
Change from baseline		
n	81	29
Mean (SD)	0.40 (3.55)	1.11 (3.22)
SE	0.39	0.60
Median	0.00	0.00
Min, Max	-13.5, 9.0	-6.0, 8.5

mNIS+7 score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurologic impairment (range = 0 to 304). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 2.8
Modified Neuropathy Impairment Score +7 (mNIS+7) Components: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Component: Neuropathy Impairment Score - Reflexes (NIS-R)

FAP Stage: II&III

Subgroup Visit	Vutrisiran (HELIOS-A) (N=38)	Patisiran (HELIOS-A) (N=11)
Baseline		
n	38	11
Mean (SD)	15.05 (5.24)	14.77 (5.66)
SE	0.85	1.71
Median	17.25	19.00
Min, Max	2.0, 20.0	7.0, 20.0
Month 9		
Actual Value		
n	35	10
Mean (SD)	14.96 (5.04)	14.40 (6.45)
SE	0.85	2.04
Median	17.00	16.00
Min, Max	6.0, 20.0	2.0, 20.0
Change from baseline		
n	35	10
Mean (SD)	-0.10 (2.17)	0.15 (3.51)
SE	0.37	1.11
Median	0.00	0.50
Min, Max	-6.0, 4.0	-8.0, 6.5

mNIS+7 score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurologic impairment (range = 0 to 304). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 2.8
Modified Neuropathy Impairment Score +7 (mNIS+7) Components: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Component: Neuropathy Impairment Score - Reflexes (NIS-R)

FAP Stage: II&III

Subgroup Visit	Vutrisiran (HELIOS-A) (N=38)	Patisiran (HELIOS-A) (N=11)
Month 18		
Actual Value		
n	34	8
Mean (SD)	15.37 (4.91)	15.58 (6.21)
SE	0.84	2.19
Median	16.50	19.50
Min, Max	5.5, 20.0	4.0, 20.0
Change from baseline		
n	34	8
Mean (SD)	0.34 (3.75)	1.14 (2.59)
SE	0.64	0.91
Median	0.00	1.00
Min, Max	-8.0, 11.0	-3.0, 6.0

mNIS+7 score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurologic impairment (range = 0 to 304). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 2.8
Modified Neuropathy Impairment Score +7 (mNIS+7) Components: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Component: Neuropathy Impairment Score - Reflexes (NIS-R)

Cardiac Subpopulation: Yes

Subgroup Visit	Vutrisiran (HELIOS-A) (N=40)	Patisiran (HELIOS-A) (N=14)
Baseline		
n	40	14
Mean (SD)	14.01 (5.58)	12.82 (7.40)
SE	0.88	1.98
Median	14.75	17.00
Min, Max	0.0, 20.0	2.5, 20.0
Month 9		
Actual Value		
n	38	14
Mean (SD)	13.71 (5.70)	12.89 (7.05)
SE	0.93	1.88
Median	14.50	14.25
Min, Max	0.0, 20.0	2.0, 20.0
Change from baseline		
n	38	14
Mean (SD)	-0.26 (2.31)	0.07 (2.79)
SE	0.38	0.75
Median	0.00	0.00
Min, Max	-6.0, 4.0	-3.5, 8.0

mNIS+7 score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurologic impairment (range = 0 to 304). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Alnylam Pharmaceuticals Inc.
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Table 2.8
Modified Neuropathy Impairment Score +7 (mNIS+7) Components: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Component: Neuropathy Impairment Score - Reflexes (NIS-R)

Cardiac Subpopulation: Yes

Subgroup Visit	Vutrisiran (HELIOS-A) (N=40)	Patisiran (HELIOS-A) (N=14)
Month 18		
Actual Value		
n	37	13
Mean (SD)	13.66 (5.57)	13.50 (7.44)
SE	0.92	2.06
Median	15.00	19.50
Min, Max	0.0, 20.0	3.0, 20.0
Change from baseline		
n	37	13
Mean (SD)	-0.15 (4.03)	1.15 (2.52)
SE	0.66	0.70
Median	0.00	1.00
Min, Max	-11.5, 8.0	-3.0, 7.5

mNIS+7 score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurologic impairment (range = 0 to 304). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 2.8
Modified Neuropathy Impairment Score +7 (mNIS+7) Components: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Component: Neuropathy Impairment Score - Reflexes (NIS-R)

Cardiac Subpopulation: No

Subgroup Visit	Vutrisiran (HELIOS-A) (N=82)	Patisiran (HELIOS-A) (N=28)
Baseline		
n	82	28
Mean (SD)	8.55 (6.20)	8.48 (6.41)
SE	0.68	1.21
Median	8.00	6.75
Min, Max	0.0, 20.0	0.0, 20.0
Month 9		
Actual Value		
n	79	26
Mean (SD)	8.58 (5.97)	7.71 (6.04)
SE	0.67	1.18
Median	7.00	6.00
Min, Max	0.0, 20.0	0.0, 20.0
Change from baseline		
n	79	26
Mean (SD)	0.16 (3.59)	0.12 (2.98)
SE	0.40	0.58
Median	0.00	0.00
Min, Max	-13.0, 18.0	-8.0, 6.5

mNIS+7 score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurologic impairment (range = 0 to 304). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 2.8
Modified Neuropathy Impairment Score +7 (mNIS+7) Components: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Component: Neuropathy Impairment Score - Reflexes (NIS-R)

Cardiac Subpopulation: No

Subgroup Visit	Vutrisiran (HELIOS-A) (N=82)	Patisiran (HELIOS-A) (N=28)
Month 18		
Actual Value		
n	78	24
Mean (SD)	8.89 (6.13)	8.36 (6.09)
SE	0.69	1.24
Median	8.00	7.00
Min, Max	0.0, 20.0	0.0, 20.0
Change from baseline		
n	78	24
Mean (SD)	0.63 (3.37)	1.09 (3.37)
SE	0.38	0.69
Median	0.00	0.50
Min, Max	-13.5, 11.0	-6.0, 8.5

mNIS+7 score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurologic impairment (range = 0 to 304). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 2.8
Modified Neuropathy Impairment Score +7 (mNIS+7) Components: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Component: Neuropathy Impairment Score - Reflexes (NIS-R)

Weight (kg): <65

Subgroup Visit	Vutrisiran (HELIOS-A) (N=46)	Patisiran (HELIOS-A) (N=15)
Baseline		
n	46	15
Mean (SD)	11.54 (6.05)	7.03 (6.16)
SE	0.89	1.59
Median	11.50	4.50
Min, Max	0.0, 20.0	0.0, 20.0
Month 9		
Actual Value		
n	44	15
Mean (SD)	11.13 (5.76)	6.63 (6.44)
SE	0.87	1.66
Median	10.75	5.50
Min, Max	0.0, 20.0	0.0, 20.0
Change from baseline		
n	44	15
Mean (SD)	-0.27 (2.66)	-0.40 (3.33)
SE	0.40	0.86
Median	0.00	0.00
Min, Max	-9.0, 5.5	-8.0, 6.5

mNIS+7 score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurologic impairment (range = 0 to 304). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 2.8
Modified Neuropathy Impairment Score +7 (mNIS+7) Components: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Component: Neuropathy Impairment Score - Reflexes (NIS-R)

Weight (kg): <65

Subgroup Visit	Vutrisiran (HELIOS-A) (N=46)	Patisiran (HELIOS-A) (N=15)
Month 18		
Actual Value		
n	42	14
Mean (SD)	11.27 (6.05)	7.37 (6.37)
SE	0.93	1.70
Median	11.00	5.50
Min, Max	0.0, 20.0	0.0, 20.0
Change from baseline		
n	42	14
Mean (SD)	0.29 (4.12)	0.91 (1.35)
SE	0.64	0.36
Median	0.00	1.06
Min, Max	-13.5, 7.5	-2.0, 3.0

mNIS+7 score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurologic impairment (range = 0 to 304). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 2.8
Modified Neuropathy Impairment Score +7 (mNIS+7) Components: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Component: Neuropathy Impairment Score - Reflexes (NIS-R)

Weight (kg): ≥65

Subgroup Visit	Vutrisiran (HELIOS-A) (N=76)	Patisiran (HELIOS-A) (N=27)
Baseline		
n	76	27
Mean (SD)	9.61 (6.71)	11.54 (6.99)
SE	0.77	1.35
Median	8.50	11.00
Min, Max	0.0, 20.0	1.5, 20.0
Month 9		
Actual Value		
n	73	25
Mean (SD)	9.72 (6.65)	11.26 (6.52)
SE	0.78	1.30
Median	8.00	9.00
Min, Max	0.0, 20.0	3.5, 20.0
Change from baseline		
n	73	25
Mean (SD)	0.21 (3.53)	0.40 (2.60)
SE	0.41	0.52
Median	0.00	0.00
Min, Max	-13.0, 18.0	-4.0, 8.0

mNIS+7 score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurologic impairment (range = 0 to 304). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 2.8
Modified Neuropathy Impairment Score +7 (mNIS+7) Components: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Component: Neuropathy Impairment Score - Reflexes (NIS-R)

Weight (kg): ≥65

Subgroup Visit	Vutrisiran (HELIOS-A) (N=76)	Patisiran (HELIOS-A) (N=27)
Month 18		
Actual Value		
n	73	23
Mean (SD)	9.94 (6.49)	11.87 (6.86)
SE	0.76	1.43
Median	8.00	10.00
Min, Max	0.0, 20.0	3.0, 20.0
Change from baseline		
n	73	23
Mean (SD)	0.44 (3.29)	1.24 (3.77)
SE	0.38	0.79
Median	0.00	0.00
Min, Max	-11.5, 11.0	-6.0, 8.5

mNIS+7 score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurologic impairment (range = 0 to 304). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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mNIS+7 – Domäne *Quantitative Sensory Testing*

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Table 2.6
Modified Neuropathy Impairment Score +7 (mNIS+7) Component Scores: Change from Baseline to Month 18, MMRM Model
Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A) Subgroup Analysis
mITT Population

Quantitative Sensory Testing (QST)

Subgroup Visit	LS Mean (95% CI) Vutrisiran (HELIOS-A) (N=122)	LS Mean (95% CI) Patisiran (HELIOS-A) (N=42)	LS Mean Difference (Vutrisiran-Patisiran) (95% CI), p-value	Standardized Effect Size (95% CI)
Age (years)				
<65	75	30		
Month 9	-2.15 (-4.51, 0.22)	0.79 (-2.99, 4.58)	-2.94 (-7.41, 1.53), 0.1955	-0.26 (-0.69, 0.16)
Month 18	-2.48 (-4.82, -0.14)	0.04 (-3.73, 3.81)	-2.53 (-6.97, 1.92), 0.2635	-0.24 (-0.66, 0.19)
≥65	44	10		
Month 9	0.93 (-2.07, 3.93)	-5.47 (-11.68, 0.74)	6.40 (-0.50, 13.30), 0.0689	0.65 (-0.03, 1.34)
Month 18	0.59 (-2.41, 3.59)	-6.22 (-12.46, 0.02)	6.81 (-0.11, 13.74), 0.0538	0.67 (-0.05, 1.39)
p-value of Treatment*Age	0.0201			

mNIS+7 score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurologic impairment (range = 0 to 304). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.
LS estimates and p-value derived from mixed-effects model for repeated measures (MMRM), controlling for categorical factors (treatment, visit), the subgroup variable, continuous covariate (baseline value), and interaction (treatment by visit, treatment by subgroup).
Standardized effect size (d) = LS mean difference/estimated pooled standard deviation with the small sample bias correction.

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Table 2.6
Modified Neuropathy Impairment Score +7 (mNIS+7) Component Scores: Change from Baseline to Month 18, MMRM Model
Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A) Subgroup Analysis
mITT Population

Quantitative Sensory Testing (QST)

Subgroup Visit	LS Mean (95% CI) Vutrisiran (HELIOS-A) (N=122)	LS Mean (95% CI) Patisiran (HELIOS-A) (N=42)	LS Mean Difference (Vutrisiran-Patisiran) (95% CI), p-value	Standardized Effect Size (95% CI)
Sex				
Male	77	25		
Month 9	0.54 (-1.78, 2.86)	0.20 (-3.88, 4.27)	0.34 (-4.36, 5.04), 0.8857	0.03 (-0.41, 0.48)
Month 18	0.20 (-2.14, 2.53)	-0.51 (-4.65, 3.64)	0.70 (-4.06, 5.47), 0.7713	0.07 (-0.40, 0.53)
Female	42	15		
Month 9	-3.87 (-6.92, -0.82)	-2.38 (-7.47, 2.72)	-1.49 (-7.43, 4.45), 0.6206	-0.13 (-0.71, 0.46)
Month 18	-4.21 (-7.26, -1.16)	-3.08 (-8.17, 2.02)	-1.13 (-7.07, 4.81), 0.7074	-0.10 (-0.69, 0.48)
p-value of Treatment*Sex	0.6155			

mNIS+7 score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurologic impairment (range = 0 to 304). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.
LS estimates and p-value derived from mixed-effects model for repeated measures (MMRM), controlling for categorical factors (treatment, visit), the subgroup variable, continuous covariate (baseline value), and interaction (treatment by visit, treatment by subgroup).
Standardized effect size (d) = LS mean difference/estimated pooled standard deviation with the small sample bias correction.

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Table 2.6
Modified Neuropathy Impairment Score +7 (mNIS+7) Component Scores: Change from Baseline to Month 18, MMRM Model
Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A) Subgroup Analysis
mITT Population

Quantitative Sensory Testing (QST)

Subgroup Visit	LS Mean (95% CI) Vutrisiran (HELIOS-A) (N=122)	LS Mean (95% CI) Patisiran (HELIOS-A) (N=42)	LS Mean Difference (Vutrisiran-Patisiran) (95% CI), p-value	Standardized Effect Size (95% CI)
Race				
White	84	28		
Month 9	-0.01 (-2.26, 2.25)	-0.18 (-4.08, 3.71)	0.18 (-4.33, 4.68), 0.9381	0.02 (-0.41, 0.44)
Month 18	-0.37 (-2.63, 1.90)	-0.91 (-4.83, 3.01)	0.55 (-3.98, 5.08), 0.8123	0.05 (-0.38, 0.48)
All Other Races	35	12		
Month 9	-3.42 (-6.78, -0.06)	-2.20 (-8.00, 3.59)	-1.22 (-7.92, 5.49), 0.7201	-0.12 (-0.77, 0.53)
Month 18	-3.78 (-7.15, -0.41)	-2.93 (-8.77, 2.91)	-0.85 (-7.60, 5.90), 0.8039	-0.08 (-0.75, 0.59)
p-value of Treatment*Race	0.7214			

mNIS+7 score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurologic impairment (range = 0 to 304). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.
LS estimates and p-value derived from mixed-effects model for repeated measures (MMRM), controlling for categorical factors (treatment, visit), the subgroup variable, continuous covariate (baseline value), and interaction (treatment by visit, treatment by subgroup).
Standardized effect size (d) = LS mean difference/estimated pooled standard deviation with the small sample bias correction.

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Table 2.6
Modified Neuropathy Impairment Score +7 (mNIS+7) Component Scores: Change from Baseline to Month 18, MMRM Model
Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A) Subgroup Analysis
mITT Population

Quantitative Sensory Testing (QST)

Subgroup Visit	LS Mean (95% CI) Vutrisiran (HELIOS-A) (N=122)	LS Mean (95% CI) Patisiran (HELIOS-A) (N=42)	LS Mean Difference (Vutrisiran-Patisiran) (95% CI), p-value	Standardized Effect Size (95% CI)
Region				
North America	27	8		
Month 9	-5.52 (-9.34, -1.70)	-5.69 (-12.52, 1.14)	0.17 (-7.64, 7.98), 0.9657	0.02 (-0.76, 0.79)
Month 18	-5.85 (-9.65, -2.05)	-6.43 (-13.29, 0.43)	0.59 (-7.25, 8.42), 0.8828	0.07 (-0.74, 0.89)
Western Europe	40	18		
Month 9	-1.24 (-4.33, 1.85)	-0.37 (-5.03, 4.29)	-0.87 (-6.47, 4.73), 0.7587	-0.09 (-0.64, 0.46)
Month 18	-1.57 (-4.64, 1.49)	-1.12 (-5.73, 3.50)	-0.46 (-6.00, 5.09), 0.8710	-0.05 (-0.60, 0.50)
Rest of World	52	14		
Month 9	1.50 (-1.27, 4.26)	1.21 (-4.08, 6.50)	0.29 (-5.73, 6.31), 0.9248	0.02 (-0.56, 0.61)
Month 18	1.17 (-1.59, 3.93)	0.47 (-4.83, 5.76)	0.70 (-5.32, 6.72), 0.8178	0.06 (-0.54, 0.66)
p-value of Treatment*Region	0.9510			

mNIS+7 score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurologic impairment (range = 0 to 304). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.
LS estimates and p-value derived from mixed-effects model for repeated measures (MMRM), controlling for categorical factors (treatment, visit), the subgroup variable, continuous covariate (baseline value), and interaction (treatment by visit, treatment by subgroup).
Standardized effect size (d) = LS mean difference/estimated pooled standard deviation with the small sample bias correction.

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Table 2.6
Modified Neuropathy Impairment Score +7 (mNIS+7) Component Scores: Change from Baseline to Month 18, MMRM Model
Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A) Subgroup Analysis
mITT Population

Quantitative Sensory Testing (QST)

Subgroup Visit	LS Mean (95% CI) Vutrisiran (HELIOS-A) (N=122)	LS Mean (95% CI) Patisiran (HELIOS-A) (N=42)	LS Mean Difference (Vutrisiran-Patisiran) (95% CI), p-value	Standardized Effect Size (95% CI)
Baseline NIS				
<50	77	27		
Month 9	-3.40 (-5.70, -1.09)	-2.17 (-6.08, 1.73)	-1.23 (-5.72, 3.27), 0.5914	-0.12 (-0.55, 0.32)
Month 18	-3.75 (-6.03, -1.47)	-2.87 (-6.74, 1.00)	-0.88 (-5.34, 3.57), 0.6965	-0.09 (-0.53, 0.35)
≥50	42	13		
Month 9	3.58 (0.47, 6.69)	1.47 (-3.88, 6.83)	2.11 (-4.08, 8.29), 0.5026	0.20 (-0.42, 0.82)
Month 18	3.22 (0.14, 6.31)	0.77 (-4.58, 6.13)	2.45 (-3.72, 8.62), 0.4345	0.22 (-0.41, 0.86)
p-value of Treatment*Baseline NIS	0.3640			

mNIS+7 score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurologic impairment (range = 0 to 304). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.
LS estimates and p-value derived from mixed-effects model for repeated measures (MMRM), controlling for categorical factors (treatment, visit), the subgroup variable, continuous covariate (baseline value), and interaction (treatment by visit, treatment by subgroup).
Standardized effect size (d) = LS mean difference/estimated pooled standard deviation with the small sample bias correction.

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Table 2.6
Modified Neuropathy Impairment Score +7 (mNIS+7) Component Scores: Change from Baseline to Month 18, MMRM Model
Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A) Subgroup Analysis
mITT Population

Quantitative Sensory Testing (QST)

Subgroup Visit	LS Mean (95% CI) Vutrisiran (HELIOS-A) (N=122)	LS Mean (95% CI) Patisiran (HELIOS-A) (N=42)	LS Mean Difference (Vutrisiran-Patisiran) (95% CI), p-value	Standardized Effect Size (95% CI)
Previous Tetramer Stabilizer Use				
Yes	74	32		
Month 9	-2.35 (-4.74, 0.04)	-0.35 (-4.05, 3.34)	-2.00 (-6.40, 2.41), 0.3729	-0.18 (-0.60, 0.23)
Month 18	-2.72 (-5.12, -0.33)	-1.09 (-4.77, 2.60)	-1.64 (-6.04, 2.77), 0.4642	-0.16 (-0.58, 0.26)
No	45	8		
Month 9	1.21 (-1.79, 4.21)	-2.31 (-9.34, 4.71)	3.53 (-4.09, 11.14), 0.3620	0.33 (-0.41, 1.08)
Month 18	0.84 (-2.14, 3.81)	-3.05 (-10.11, 4.02)	3.89 (-3.76, 11.53), 0.3172	0.35 (-0.44, 1.14)
p-value of Treatment*Previous Tetramer Stabilizer Use	0.1984			

mNIS+7 score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurologic impairment (range = 0 to 304). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.
LS estimates and p-value derived from mixed-effects model for repeated measures (MMRM), controlling for categorical factors (treatment, visit), the subgroup variable, continuous covariate (baseline value), and interaction (treatment by visit, treatment by subgroup).
Standardized effect size (d) = LS mean difference/estimated pooled standard deviation with the small sample bias correction.

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Table 2.6
Modified Neuropathy Impairment Score +7 (mNIS+7) Component Scores: Change from Baseline to Month 18, MMRM Model
Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A) Subgroup Analysis
mITT Population

Quantitative Sensory Testing (QST)

Subgroup Visit	LS Mean (95% CI) Vutrisiran (HELIOS-A) (N=122)	LS Mean (95% CI) Patisiran (HELIOS-A) (N=42)	LS Mean Difference (Vutrisiran-Patisiran) (95% CI), p-value	Standardized Effect Size (95% CI)
Genotype				
V30M	53	20		
Month 9	-1.14 (-3.97, 1.69)	-0.21 (-4.78, 4.35)	-0.92 (-6.29, 4.45), 0.7348	-0.09 (-0.60, 0.42)
Month 18	-1.49 (-4.31, 1.33)	-0.94 (-5.49, 3.60)	-0.55 (-5.89, 4.80), 0.8399	-0.06 (-0.57, 0.45)
non-V30M	66	20		
Month 9	-0.90 (-3.45, 1.64)	-1.34 (-5.97, 3.28)	0.44 (-4.81, 5.69), 0.8688	0.04 (-0.46, 0.54)
Month 18	-1.26 (-3.80, 1.28)	-2.08 (-6.76, 2.60)	0.82 (-4.48, 6.11), 0.7617	0.07 (-0.45, 0.59)
p-value of Treatment*Genotype	0.7051			

mNIS+7 score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurologic impairment (range = 0 to 304). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.
LS estimates and p-value derived from mixed-effects model for repeated measures (MMRM), controlling for categorical factors (treatment, visit), the subgroup variable, continuous covariate (baseline value), and interaction (treatment by visit, treatment by subgroup).
Standardized effect size (d) = LS mean difference/estimated pooled standard deviation with the small sample bias correction.

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Table 2.6
Modified Neuropathy Impairment Score +7 (mNIS+7) Component Scores: Change from Baseline to Month 18, MMRM Model
Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A) Subgroup Analysis
mITT Population

Quantitative Sensory Testing (QST)

Subgroup Visit	LS Mean (95% CI) Vutrisiran (HELIOS-A) (N=122)	LS Mean (95% CI) Patisiran (HELIOS-A) (N=42)	LS Mean Difference (Vutrisiran-Patisiran) (95% CI), p-value	Standardized Effect Size (95% CI)
FAP Stage				
I	83	30		
Month 9	-2.69 (-4.93, -0.45)	-0.90 (-4.67, 2.88)	-1.80 (-6.19, 2.59), 0.4199	-0.17 (-0.58, 0.25)
Month 18	-3.04 (-5.27, -0.80)	-1.61 (-5.37, 2.15)	-1.43 (-5.80, 2.94), 0.5202	-0.14 (-0.55, 0.28)
II&III	36	10		
Month 9	2.92 (-0.36, 6.20)	-0.56 (-6.75, 5.63)	3.48 (-3.52, 10.47), 0.3277	0.33 (-0.36, 1.02)
Month 18	2.58 (-0.70, 5.86)	-1.27 (-7.57, 5.02)	3.85 (-3.23, 10.94), 0.2850	0.35 (-0.41, 1.11)
p-value of Treatment*FAP Stage	0.1914			

mNIS+7 score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurologic impairment (range = 0 to 304). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.
LS estimates and p-value derived from mixed-effects model for repeated measures (MMRM), controlling for categorical factors (treatment, visit), the subgroup variable, continuous covariate (baseline value), and interaction (treatment by visit, treatment by subgroup).
Standardized effect size (d) = LS mean difference/estimated pooled standard deviation with the small sample bias correction.

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Table 2.6
Modified Neuropathy Impairment Score +7 (mNIS+7) Component Scores: Change from Baseline to Month 18, MMRM Model
Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A) Subgroup Analysis
mITT Population

Quantitative Sensory Testing (QST)

Subgroup Visit	LS Mean (95% CI) Vutrisiran (HELIOS-A) (N=122)	LS Mean (95% CI) Patisiran (HELIOS-A) (N=42)	LS Mean Difference (Vutrisiran-Patisiran) (95% CI), p-value	Standardized Effect Size (95% CI)
Cardiac Subpopulation				
Yes	38	14		
Month 9	3.14 (-0.01, 6.29)	1.85 (-3.39, 7.09)	1.29 (-4.83, 7.40), 0.6783	0.12 (-0.48, 0.73)
Month 18	2.80 (-0.32, 5.92)	1.14 (-4.07, 6.36)	1.66 (-4.42, 7.74), 0.5911	0.14 (-0.49, 0.76)
No	81	26		
Month 9	-2.98 (-5.25, -0.72)	-2.15 (-6.13, 1.82)	-0.83 (-5.41, 3.75), 0.7213	-0.08 (-0.52, 0.36)
Month 18	-3.32 (-5.54, -1.10)	-2.86 (-6.78, 1.05)	-0.46 (-4.96, 4.05), 0.8413	-0.05 (-0.50, 0.40)
p-value of Treatment*Cardiac Subpopulation	0.5623			

mNIS+7 score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurologic impairment (range = 0 to 304). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.
LS estimates and p-value derived from mixed-effects model for repeated measures (MMRM), controlling for categorical factors (treatment, visit), the subgroup variable, continuous covariate (baseline value), and interaction (treatment by visit, treatment by subgroup).
Standardized effect size (d) = LS mean difference/estimated pooled standard deviation with the small sample bias correction.

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Table 2.6
Modified Neuropathy Impairment Score +7 (mNIS+7) Component Scores: Change from Baseline to Month 18, MMRM Model
Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A) Subgroup Analysis
mITT Population

Quantitative Sensory Testing (QST)

Subgroup Visit	LS Mean (95% CI) Vutrisiran (HELIOS-A) (N=122)	LS Mean (95% CI) Patisiran (HELIOS-A) (N=42)	LS Mean Difference (Vutrisiran-Patisiran) (95% CI), p-value	Standardized Effect Size (95% CI)
Weight (kg)				
<65	44	15		
Month 9	-0.02 (-3.07, 3.04)	1.79 (-3.38, 6.96)	-1.81 (-7.83, 4.21), 0.5541	-0.18 (-0.76, 0.40)
Month 18	-0.36 (-3.42, 2.69)	1.04 (-4.10, 6.18)	-1.40 (-7.39, 4.58), 0.6439	-0.15 (-0.74, 0.43)
≥65	75	25		
Month 9	-1.58 (-3.98, 0.81)	-2.37 (-6.51, 1.77)	0.79 (-3.98, 5.56), 0.7449	0.07 (-0.38, 0.52)
Month 18	-1.93 (-4.30, 0.44)	-3.12 (-7.29, 1.05)	1.19 (-3.59, 5.97), 0.6237	0.10 (-0.36, 0.57)
p-value of Treatment*Weight	0.4815			

mNIS+7 score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurologic impairment (range = 0 to 304). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.
LS estimates and p-value derived from mixed-effects model for repeated measures (MMRM), controlling for categorical factors (treatment, visit), the subgroup variable, continuous covariate (baseline value), and interaction (treatment by visit, treatment by subgroup).
Standardized effect size (d) = LS mean difference/estimated pooled standard deviation with the small sample bias correction.

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Table 2.8
Modified Neuropathy Impairment Score +7 (mNIS+7) Components: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Component: Quantitative Sensory Testing (QST)

Age (years): <65

Subgroup Visit	Vutrisiran (HELIOS-A) (N=76)	Patisiran (HELIOS-A) (N=31)
Baseline		
n	76	31
Mean (SD)	23.20 (17.72)	19.52 (14.33)
SE	2.03	2.57
Median	21.50	16.00
Min, Max	0.0, 72.0	0.0, 49.0
Month 9		
Actual Value		
n	74	30
Mean (SD)	20.77 (18.31)	19.77 (16.63)
SE	2.13	3.04
Median	17.50	17.00
Min, Max	0.0, 68.0	0.0, 63.0
Change from baseline		
n	74	30
Mean (SD)	-2.11 (11.66)	1.23 (10.75)
SE	1.36	1.96
Median	0.00	-0.50
Min, Max	-28.1, 36.0	-33.0, 29.0

mNIS+7 score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurologic impairment (range = 0 to 304). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 2.8
Modified Neuropathy Impairment Score +7 (mNIS+7) Components: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Component: Quantitative Sensory Testing (QST)

Age (years): <65

Subgroup Visit	Vutrisiran (HELIOS-A) (N=76)	Patisiran (HELIOS-A) (N=31)
Month 18		
Actual Value		
n	74	29
Mean (SD)	20.65 (17.73)	18.96 (14.64)
SE	2.06	2.72
Median	16.50	16.00
Min, Max	0.0, 63.0	0.0, 52.0
Change from baseline		
n	74	29
Mean (SD)	-2.77 (11.54)	0.51 (10.18)
SE	1.34	1.89
Median	-2.00	0.00
Min, Max	-33.0, 31.0	-34.0, 28.0

mNIS+7 score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurologic impairment (range = 0 to 304). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 2.8
Modified Neuropathy Impairment Score +7 (mNIS+7) Components: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Component: Quantitative Sensory Testing (QST)

Age (years): ≥65

Subgroup Visit	Vutrisiran (HELIOS-A) (N=46)	Patisiran (HELIOS-A) (N=11)
Baseline		
n	46	11
Mean (SD)	22.67 (17.26)	19.98 (15.03)
SE	2.54	4.53
Median	19.00	16.00
Min, Max	0.0, 74.0	0.0, 42.0
Month 9		
Actual Value		
n	43	10
Mean (SD)	22.98 (20.20)	12.80 (12.38)
SE	3.08	3.92
Median	19.13	11.00
Min, Max	0.0, 66.0	0.0, 43.0
Change from baseline		
n	43	10
Mean (SD)	0.42 (9.74)	-5.08 (9.29)
SE	1.48	2.94
Median	0.00	-5.00
Min, Max	-29.0, 25.0	-24.0, 7.0

mNIS+7 score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurologic impairment (range = 0 to 304). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 2.8
Modified Neuropathy Impairment Score +7 (mNIS+7) Components: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Component: Quantitative Sensory Testing (QST)

Age (years): ≥65

Subgroup Visit	Vutrisiran (HELIOS-A) (N=46)	Patisiran (HELIOS-A) (N=11)
Month 18		
Actual Value		
n	41	9
Mean (SD)	23.49 (22.07)	13.45 (11.83)
SE	3.45	3.94
Median	19.00	7.00
Min, Max	0.0, 78.0	0.0, 39.0
Change from baseline		
n	41	9
Mean (SD)	1.44 (9.82)	-6.41 (6.64)
SE	1.53	2.21
Median	0.00	-4.00
Min, Max	-16.0, 37.0	-18.0, 4.0

mNIS+7 score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurologic impairment (range = 0 to 304). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 2.8
Modified Neuropathy Impairment Score +7 (mNIS+7) Components: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Component: Quantitative Sensory Testing (QST)

Sex: Male

Subgroup Visit	Vutrisiran (HELIOS-A) (N=79)	Patisiran (HELIOS-A) (N=27)
Baseline		
n	79	27
Mean (SD)	23.23 (17.01)	18.70 (13.64)
SE	1.91	2.62
Median	20.00	16.00
Min, Max	0.0, 74.0	0.0, 49.0
Month 9		
Actual Value		
n	76	25
Mean (SD)	23.67 (17.62)	17.24 (15.58)
SE	2.02	3.12
Median	20.50	17.00
Min, Max	0.0, 66.0	0.0, 63.0
Change from baseline		
n	76	25
Mean (SD)	0.74 (10.36)	0.65 (9.30)
SE	1.19	1.86
Median	1.57	-1.00
Min, Max	-29.0, 25.0	-12.0, 29.0

mNIS+7 score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurologic impairment (range = 0 to 304). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 2.8
Modified Neuropathy Impairment Score +7 (mNIS+7) Components: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Component: Quantitative Sensory Testing (QST)

Sex: Male

Subgroup Visit	Vutrisiran (HELIOS-A) (N=79)	Patisiran (HELIOS-A) (N=27)
Month 18		
Actual Value		
n	74	23
Mean (SD)	22.91 (18.99)	17.39 (13.55)
SE	2.21	2.83
Median	21.00	16.00
Min, Max	0.0, 78.0	0.0, 52.0
Change from baseline		
n	74	23
Mean (SD)	0.07 (11.22)	0.27 (6.84)
SE	1.30	1.43
Median	0.00	0.00
Min, Max	-26.0, 37.0	-12.0, 19.0

mNIS+7 score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurologic impairment (range = 0 to 304). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 2.8
Modified Neuropathy Impairment Score +7 (mNIS+7) Components: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Component: Quantitative Sensory Testing (QST)

Sex: Female

Subgroup Visit	Vutrisiran (HELIOS-A) (N=43)	Patisiran (HELIOS-A) (N=15)
Baseline		
n	43	15
Mean (SD)	22.58 (18.51)	21.33 (15.85)
SE	2.82	4.09
Median	21.00	16.00
Min, Max	0.0, 72.0	0.0, 48.0
Month 9		
Actual Value		
n	41	15
Mean (SD)	17.71 (20.91)	19.33 (16.69)
SE	3.27	4.31
Median	10.00	14.00
Min, Max	0.0, 68.0	0.0, 49.0
Change from baseline		
n	41	15
Mean (SD)	-4.73 (11.45)	-2.00 (12.77)
SE	1.79	3.30
Median	-4.00	0.00
Min, Max	-28.0, 36.0	-33.0, 20.0

mNIS+7 score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurologic impairment (range = 0 to 304). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 2.8
Modified Neuropathy Impairment Score +7 (mNIS+7) Components: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Component: Quantitative Sensory Testing (QST)

Sex: Female

Subgroup Visit	Vutrisiran (HELIOS-A) (N=43)	Patisiran (HELIOS-A) (N=15)
Month 18		
Actual Value		
n	41	15
Mean (SD)	19.41 (20.00)	18.06 (15.32)
SE	3.12	3.96
Median	11.00	15.00
Min, Max	0.0, 66.0	0.0, 46.9
Change from baseline		
n	41	15
Mean (SD)	-3.68 (10.58)	-3.28 (13.20)
SE	1.65	3.41
Median	-2.00	-3.00
Min, Max	-33.0, 15.0	-34.0, 28.0

mNIS+7 score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurologic impairment (range = 0 to 304). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 2.8
Modified Neuropathy Impairment Score +7 (mNIS+7) Components: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Component: Quantitative Sensory Testing (QST)

Race: White

Subgroup Visit	Vutrisiran (HELIOS-A) (N=86)	Patisiran (HELIOS-A) (N=29)
Baseline		
n	86	29
Mean (SD)	23.02 (17.92)	21.66 (13.79)
SE	1.93	2.56
Median	19.50	16.00
Min, Max	0.0, 72.0	0.0, 48.0
Month 9		
Actual Value		
n	83	28
Mean (SD)	22.87 (19.61)	21.57 (16.38)
SE	2.15	3.10
Median	19.00	17.50
Min, Max	0.0, 68.0	0.0, 63.0
Change from baseline		
n	83	28
Mean (SD)	-0.11 (10.78)	0.61 (12.15)
SE	1.18	2.30
Median	0.00	0.00
Min, Max	-28.1, 36.0	-33.0, 29.0

mNIS+7 score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurologic impairment (range = 0 to 304). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 2.8
Modified Neuropathy Impairment Score +7 (mNIS+7) Components: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Component: Quantitative Sensory Testing (QST)

Race: White

Subgroup Visit	Vutrisiran (HELIOS-A) (N=86)	Patisiran (HELIOS-A) (N=29)
Month 18		
Actual Value		
n	82	27
Mean (SD)	22.71 (20.27)	19.59 (15.51)
SE	2.24	2.98
Median	20.50	18.00
Min, Max	0.0, 78.0	0.0, 52.0
Change from baseline		
n	82	27
Mean (SD)	-0.57 (11.09)	-1.38 (10.29)
SE	1.22	1.98
Median	0.00	-1.13
Min, Max	-33.0, 37.0	-34.0, 28.0

mNIS+7 score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurologic impairment (range = 0 to 304). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 2.8
Modified Neuropathy Impairment Score +7 (mNIS+7) Components: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Component: Quantitative Sensory Testing (QST)

Race: All Other Races

Subgroup Visit	Vutrisiran (HELIOS-A) (N=36)	Patisiran (HELIOS-A) (N=13)
Baseline		
n	36	13
Mean (SD)	22.94 (16.60)	15.14 (15.05)
SE	2.77	4.17
Median	21.00	8.00
Min, Max	0.0, 74.0	0.0, 49.0
Month 9		
Actual Value		
n	34	12
Mean (SD)	18.44 (17.18)	9.75 (11.07)
SE	2.95	3.20
Median	18.00	6.00
Min, Max	0.0, 60.0	0.0, 39.0
Change from baseline		
n	34	12
Mean (SD)	-3.79 (11.33)	-2.57 (5.68)
SE	1.94	1.64
Median	-1.50	-2.00
Min, Max	-29.0, 22.0	-12.0, 5.0

mNIS+7 score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurologic impairment (range = 0 to 304). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 2.8
Modified Neuropathy Impairment Score +7 (mNIS+7) Components: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Component: Quantitative Sensory Testing (QST)

Race: All Other Races

Subgroup Visit	Vutrisiran (HELIOS-A) (N=36)	Patisiran (HELIOS-A) (N=13)
Month 18		
Actual Value		
n	33	11
Mean (SD)	19.06 (16.81)	12.92 (8.54)
SE	2.93	2.58
Median	14.00	15.00
Min, Max	0.0, 51.0	0.0, 27.0
Change from baseline		
n	33	11
Mean (SD)	-3.00 (11.10)	-0.52 (9.08)
SE	1.93	2.74
Median	-5.00	0.00
Min, Max	-26.0, 20.0	-12.0, 19.0

mNIS+7 score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurologic impairment (range = 0 to 304). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 2.8
Modified Neuropathy Impairment Score +7 (mNIS+7) Components: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Component: Quantitative Sensory Testing (QST)

Region: North America

Subgroup Visit	Vutrisiran (HELIOS-A) (N=27)	Patisiran (HELIOS-A) (N=8)
Baseline		
n	27	8
Mean (SD)	14.81 (16.13)	20.47 (18.30)
SE	3.10	6.47
Median	8.00	21.89
Min, Max	0.0, 54.0	0.0, 48.0
Month 9		
Actual Value		
n	25	8
Mean (SD)	6.89 (9.09)	16.13 (18.47)
SE	1.82	6.53
Median	3.00	6.00
Min, Max	0.0, 33.0	1.0, 49.0
Change from baseline		
n	25	8
Mean (SD)	-5.55 (9.50)	-4.35 (13.16)
SE	1.90	4.65
Median	-2.00	-0.50
Min, Max	-27.0, 9.0	-33.0, 8.0

mNIS+7 score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurologic impairment (range = 0 to 304). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 2.8
Modified Neuropathy Impairment Score +7 (mNIS+7) Components: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Component: Quantitative Sensory Testing (QST)

Region: North America

Subgroup Visit	Vutrisiran (HELIOS-A) (N=27)	Patisiran (HELIOS-A) (N=8)
Month 18		
Actual Value		
n	25	7
Mean (SD)	10.81 (16.05)	14.99 (18.05)
SE	3.21	6.82
Median	2.00	6.08
Min, Max	0.0, 51.0	0.0, 46.9
Change from baseline		
n	25	7
Mean (SD)	-4.11 (6.82)	-8.40 (12.07)
SE	1.36	4.56
Median	-3.00	-3.00
Min, Max	-21.0, 13.0	-34.0, 0.0

mNIS+7 score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurologic impairment (range = 0 to 304). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

Alnylam Pharmaceuticals Inc.
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Table 2.8
Modified Neuropathy Impairment Score +7 (mNIS+7) Components: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Component: Quantitative Sensory Testing (QST)

Region: Western Europe

Subgroup Visit	Vutrisiran (HELIOS-A) (N=42)	Patisiran (HELIOS-A) (N=20)
Baseline		
n	42	20
Mean (SD)	24.15 (17.68)	23.30 (14.59)
SE	2.73	3.26
Median	21.00	16.00
Min, Max	0.0, 67.0	4.0, 49.0
Month 9		
Actual Value		
n	40	18
Mean (SD)	24.00 (18.72)	21.50 (14.13)
SE	2.96	3.33
Median	20.00	18.00
Min, Max	0.0, 66.0	0.0, 44.0
Change from baseline		
n	40	18
Mean (SD)	-0.40 (10.71)	0.61 (9.37)
SE	1.69	2.21
Median	0.57	1.00
Min, Max	-28.1, 24.0	-24.0, 16.0

mNIS+7 score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurologic impairment (range = 0 to 304). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 2.8
Modified Neuropathy Impairment Score +7 (mNIS+7) Components: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Component: Quantitative Sensory Testing (QST)

Region: Western Europe

Subgroup Visit	Vutrisiran (HELIOS-A) (N=42)	Patisiran (HELIOS-A) (N=20)
Month 18		
Actual Value		
n	40	18
Mean (SD)	21.45 (19.14)	19.22 (14.61)
SE	3.03	3.44
Median	17.50	18.00
Min, Max	0.0, 62.0	0.0, 52.0
Change from baseline		
n	40	18
Mean (SD)	-2.95 (10.92)	-1.67 (6.87)
SE	1.73	1.62
Median	-2.00	-2.00
Min, Max	-33.0, 29.0	-18.0, 8.0

mNIS+7 score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurologic impairment (range = 0 to 304). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 2.8
Modified Neuropathy Impairment Score +7 (mNIS+7) Components: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Component: Quantitative Sensory Testing (QST)

Region: Rest of World

Subgroup Visit	Vutrisiran (HELIOS-A) (N=53)	Patisiran (HELIOS-A) (N=14)
Baseline		
n	53	14
Mean (SD)	26.26 (16.95)	13.93 (10.01)
SE	2.33	2.68
Median	25.00	13.00
Min, Max	0.0, 74.0	0.0, 34.0
Month 9		
Actual Value		
n	52	14
Mean (SD)	26.79 (19.32)	14.64 (16.59)
SE	2.68	4.43
Median	23.50	12.50
Min, Max	0.0, 68.0	0.0, 63.0
Change from baseline		
n	52	14
Mean (SD)	0.33 (11.57)	0.71 (10.96)
SE	1.60	2.93
Median	0.00	-3.00
Min, Max	-29.0, 36.0	-12.0, 29.0

mNIS+7 score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurologic impairment (range = 0 to 304). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 2.8
Modified Neuropathy Impairment Score +7 (mNIS+7) Components: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Component: Quantitative Sensory Testing (QST)

Region: Rest of World

Subgroup Visit	Vutrisiran (HELIOS-A) (N=53)	Patisiran (HELIOS-A) (N=14)
Month 18		
Actual Value		
n	50	13
Mean (SD)	27.26 (18.98)	16.92 (11.71)
SE	2.68	3.25
Median	23.50	15.00
Min, Max	0.0, 78.0	0.0, 40.0
Change from baseline		
n	50	13
Mean (SD)	1.50 (12.44)	3.54 (10.19)
SE	1.76	2.83
Median	0.00	2.00
Min, Max	-26.0, 37.0	-12.0, 28.0

mNIS+7 score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurologic impairment (range = 0 to 304). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 2.8
Modified Neuropathy Impairment Score +7 (mNIS+7) Components: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Component: Quantitative Sensory Testing (QST)

Baseline NIS: <50

Subgroup Visit	Vutrisiran (HELIOS-A) (N=78)	Patisiran (HELIOS-A) (N=27)
Baseline		
n	78	27
Mean (SD)	18.78 (16.71)	16.25 (13.94)
SE	1.89	2.68
Median	14.50	14.00
Min, Max	0.0, 67.0	0.0, 48.0
Month 9		
Actual Value		
n	77	27
Mean (SD)	16.28 (18.07)	14.52 (14.92)
SE	2.06	2.87
Median	10.00	10.00
Min, Max	0.0, 68.0	0.0, 49.0
Change from baseline		
n	77	27
Mean (SD)	-2.54 (11.28)	-1.73 (8.95)
SE	1.29	1.72
Median	-1.00	-2.00
Min, Max	-28.1, 36.0	-33.0, 16.0

mNIS+7 score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurologic impairment (range = 0 to 304). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 2.8
Modified Neuropathy Impairment Score +7 (mNIS+7) Components: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Component: Quantitative Sensory Testing (QST)

Baseline NIS: <50

Subgroup Visit	Vutrisiran (HELIOS-A) (N=78)	Patisiran (HELIOS-A) (N=27)
Month 18		
Actual Value		
n	75	26
Mean (SD)	15.55 (17.80)	15.34 (14.98)
SE	2.06	2.94
Median	9.00	11.50
Min, Max	0.0, 66.0	0.0, 52.0
Change from baseline		
n	75	26
Mean (SD)	-3.41 (10.50)	-1.53 (9.18)
SE	1.21	1.80
Median	-2.00	-1.00
Min, Max	-33.0, 31.0	-34.0, 19.0

mNIS+7 score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurologic impairment (range = 0 to 304). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 2.8
Modified Neuropathy Impairment Score +7 (mNIS+7) Components: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Component: Quantitative Sensory Testing (QST)

Baseline NIS: ≥50

Subgroup Visit	Vutrisiran (HELIOS-A) (N=44)	Patisiran (HELIOS-A) (N=15)
Baseline		
n	44	15
Mean (SD)	30.48 (16.44)	25.73 (13.37)
SE	2.48	3.45
Median	29.50	21.00
Min, Max	0.0, 74.0	7.0, 49.0
Month 9		
Actual Value		
n	40	13
Mean (SD)	31.80 (16.45)	25.31 (15.70)
SE	2.60	4.35
Median	29.50	18.00
Min, Max	4.0, 66.0	4.0, 63.0
Change from baseline		
n	40	13
Mean (SD)	1.45 (10.11)	2.54 (13.49)
SE	1.60	3.74
Median	2.00	1.00
Min, Max	-29.0, 25.0	-24.0, 29.0

mNIS+7 score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurologic impairment (range = 0 to 304). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 2.8
Modified Neuropathy Impairment Score +7 (mNIS+7) Components: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Component: Quantitative Sensory Testing (QST)

Baseline NIS: ≥50

Subgroup Visit	Vutrisiran (HELIOS-A) (N=44)	Patisiran (HELIOS-A) (N=15)
Month 18		
Actual Value		
n	40	12
Mean (SD)	33.13 (16.90)	22.67 (10.79)
SE	2.67	3.11
Median	31.00	20.50
Min, Max	5.0, 78.0	7.0, 40.0
Change from baseline		
n	40	12
Mean (SD)	2.75 (11.21)	-0.25 (11.52)
SE	1.77	3.33
Median	2.00	-2.00
Min, Max	-24.0, 37.0	-18.0, 28.0

mNIS+7 score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurologic impairment (range = 0 to 304). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 2.8
Modified Neuropathy Impairment Score +7 (mNIS+7) Components: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Component: Quantitative Sensory Testing (QST)

Previous Tetramer Stabilizer Use: Yes

Subgroup Visit	Vutrisiran (HELIOS-A) (N=75)	Patisiran (HELIOS-A) (N=33)
Baseline		
n	75	33
Mean (SD)	24.67 (18.43)	21.03 (13.84)
SE	2.13	2.41
Median	21.00	16.00
Min, Max	0.0, 74.0	3.0, 49.0
Month 9		
Actual Value		
n	74	32
Mean (SD)	22.22 (18.29)	19.91 (16.01)
SE	2.13	2.83
Median	19.00	17.00
Min, Max	0.0, 68.0	0.0, 63.0
Change from baseline		
n	74	32
Mean (SD)	-2.58 (11.07)	-0.25 (11.55)
SE	1.29	2.04
Median	0.00	-1.50
Min, Max	-29.0, 36.0	-33.0, 29.0

mNIS+7 score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurologic impairment (range = 0 to 304). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 2.8
Modified Neuropathy Impairment Score +7 (mNIS+7) Components: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Component: Quantitative Sensory Testing (QST)

Previous Tetramer Stabilizer Use: Yes

Subgroup Visit	Vutrisiran (HELIOS-A) (N=75)	Patisiran (HELIOS-A) (N=33)
Month 18		
Actual Value		
n	71	31
Mean (SD)	21.52 (18.00)	19.42 (14.17)
SE	2.14	2.54
Median	20.00	16.00
Min, Max	0.0, 66.0	0.0, 52.0
Change from baseline		
n	71	31
Mean (SD)	-2.82 (10.91)	-0.71 (10.65)
SE	1.29	1.91
Median	-1.00	-1.13
Min, Max	-33.0, 31.0	-34.0, 28.0

mNIS+7 score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurologic impairment (range = 0 to 304). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 2.8
Modified Neuropathy Impairment Score +7 (mNIS+7) Components: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Component: Quantitative Sensory Testing (QST)

Previous Tetramer Stabilizer Use: No

Subgroup Visit	Vutrisiran (HELIOS-A) (N=47)	Patisiran (HELIOS-A) (N=9)
Baseline		
n	47	9
Mean (SD)	20.34 (15.66)	14.53 (15.78)
SE	2.28	5.26
Median	17.00	14.00
Min, Max	0.0, 54.0	0.0, 41.0
Month 9		
Actual Value		
n	43	8
Mean (SD)	20.49 (20.25)	10.50 (13.36)
SE	3.09	4.72
Median	13.00	6.00
Min, Max	0.0, 66.0	0.0, 40.0
Change from baseline		
n	43	8
Mean (SD)	1.23 (10.63)	-0.72 (6.45)
SE	1.62	2.28
Median	0.00	0.00
Min, Max	-25.0, 25.0	-10.8, 8.0

mNIS+7 score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurologic impairment (range = 0 to 304). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 2.8
Modified Neuropathy Impairment Score +7 (mNIS+7) Components: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Component: Quantitative Sensory Testing (QST)

Previous Tetramer Stabilizer Use: No

Subgroup Visit	Vutrisiran (HELIOS-A) (N=47)	Patisiran (HELIOS-A) (N=9)
Month 18		
Actual Value		
n	44	7
Mean (SD)	21.89 (21.54)	9.87 (11.46)
SE	3.25	4.33
Median	13.00	6.08
Min, Max	0.0, 78.0	0.0, 31.0
Change from baseline		
n	44	7
Mean (SD)	1.23 (11.07)	-2.96 (4.98)
SE	1.67	1.88
Median	-1.00	-1.00
Min, Max	-21.0, 37.0	-11.7, 2.0

mNIS+7 score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurologic impairment (range = 0 to 304). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 2.8
Modified Neuropathy Impairment Score +7 (mNIS+7) Components: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Component: Quantitative Sensory Testing (QST)

Genotype: V30M

Subgroup Visit	Vutrisiran (HELIOS-A) (N=54)	Patisiran (HELIOS-A) (N=20)
Baseline		
n	54	20
Mean (SD)	26.72 (19.61)	22.45 (12.21)
SE	2.67	2.73
Median	21.00	17.50
Min, Max	0.0, 74.0	8.0, 45.0
Month 9		
Actual Value		
n	52	20
Mean (SD)	25.49 (19.56)	22.85 (13.13)
SE	2.71	2.94
Median	21.00	18.00
Min, Max	0.0, 68.0	4.0, 44.0
Change from baseline		
n	52	20
Mean (SD)	-0.94 (11.16)	0.40 (9.41)
SE	1.55	2.10
Median	0.07	1.00
Min, Max	-29.0, 36.0	-24.0, 16.0

mNIS+7 score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurologic impairment (range = 0 to 304). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 2.8
Modified Neuropathy Impairment Score +7 (mNIS+7) Components: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Component: Quantitative Sensory Testing (QST)

Genotype: V30M

Subgroup Visit	Vutrisiran (HELIOS-A) (N=54)	Patisiran (HELIOS-A) (N=20)
Month 18		
Actual Value		
n	52	20
Mean (SD)	23.68 (20.14)	20.85 (12.93)
SE	2.79	2.89
Median	20.50	18.00
Min, Max	0.0, 78.0	4.0, 52.0
Change from baseline		
n	52	20
Mean (SD)	-2.36 (10.89)	-1.60 (6.59)
SE	1.51	1.47
Median	-1.00	-1.50
Min, Max	-33.0, 37.0	-18.0, 8.0

mNIS+7 score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurologic impairment (range = 0 to 304). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 2.8
Modified Neuropathy Impairment Score +7 (mNIS+7) Components: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Component: Quantitative Sensory Testing (QST)

Genotype: non-V30M

Subgroup Visit	Vutrisiran (HELIOS-A) (N=68)	Patisiran (HELIOS-A) (N=22)
Baseline		
n	68	22
Mean (SD)	20.05 (15.08)	17.08 (15.87)
SE	1.83	3.38
Median	18.00	14.00
Min, Max	0.0, 54.0	0.0, 49.0
Month 9		
Actual Value		
n	65	20
Mean (SD)	18.46 (18.03)	13.20 (17.11)
SE	2.24	3.83
Median	13.00	6.00
Min, Max	0.0, 66.0	0.0, 63.0
Change from baseline		
n	65	20
Mean (SD)	-1.37 (10.99)	-1.09 (11.97)
SE	1.36	2.68
Median	0.00	-2.50
Min, Max	-28.1, 24.0	-33.0, 29.0

mNIS+7 score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurologic impairment (range = 0 to 304). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 2.8
Modified Neuropathy Impairment Score +7 (mNIS+7) Components: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Component: Quantitative Sensory Testing (QST)

Genotype: non-V30M

Subgroup Visit	Vutrisiran (HELIOS-A) (N=68)	Patisiran (HELIOS-A) (N=22)
Month 18		
Actual Value		
n	63	18
Mean (SD)	20.00 (18.65)	14.11 (14.80)
SE	2.35	3.49
Median	14.00	9.04
Min, Max	0.0, 63.0	0.0, 46.9
Change from baseline		
n	63	18
Mean (SD)	-0.37 (11.28)	-0.60 (12.71)
SE	1.42	3.00
Median	-2.00	-0.56
Min, Max	-26.0, 31.0	-34.0, 28.0

mNIS+7 score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurologic impairment (range = 0 to 304). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 2.8
Modified Neuropathy Impairment Score +7 (mNIS+7) Components: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Component: Quantitative Sensory Testing (QST)

FAP Stage: I

Subgroup Visit	Vutrisiran (HELIOS-A) (N=84)	Patisiran (HELIOS-A) (N=31)
Baseline		
n	84	31
Mean (SD)	22.24 (18.91)	17.19 (13.73)
SE	2.06	2.47
Median	19.00	14.00
Min, Max	0.0, 74.0	0.0, 48.0
Month 9		
Actual Value		
n	82	30
Mean (SD)	19.17 (19.56)	15.60 (14.45)
SE	2.16	2.64
Median	13.00	11.50
Min, Max	0.0, 68.0	0.0, 49.0
Change from baseline		
n	82	30
Mean (SD)	-2.75 (11.38)	-0.80 (9.52)
SE	1.26	1.74
Median	-1.00	-1.50
Min, Max	-29.0, 36.0	-33.0, 20.0

mNIS+7 score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurologic impairment (range = 0 to 304). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 2.8
Modified Neuropathy Impairment Score +7 (mNIS+7) Components: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Component: Quantitative Sensory Testing (QST)

FAP Stage: I

Subgroup Visit	Vutrisiran (HELIOS-A) (N=84)	Patisiran (HELIOS-A) (N=31)
Month 18		
Actual Value		
n	81	30
Mean (SD)	19.11 (19.61)	16.10 (14.62)
SE	2.18	2.67
Median	11.00	12.00
Min, Max	0.0, 66.0	0.0, 52.0
Change from baseline		
n	81	30
Mean (SD)	-2.74 (10.71)	-0.30 (10.23)
SE	1.19	1.87
Median	-1.85	-1.00
Min, Max	-33.0, 31.0	-34.0, 28.0

mNIS+7 score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurologic impairment (range = 0 to 304). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

Alnylam Pharmaceuticals Inc.
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Table 2.8
Modified Neuropathy Impairment Score +7 (mNIS+7) Components: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Component: Quantitative Sensory Testing (QST)

FAP Stage: II&III

Subgroup Visit	Vutrisiran (HELIOS-A) (N=38)	Patisiran (HELIOS-A) (N=11)
Baseline		
n	38	11
Mean (SD)	24.68 (13.85)	26.53 (14.35)
SE	2.25	4.33
Median	23.50	21.00
Min, Max	0.0, 72.0	0.0, 49.0
Month 9		
Actual Value		
n	35	10
Mean (SD)	27.23 (16.40)	25.30 (18.29)
SE	2.77	5.78
Median	27.00	17.50
Min, Max	2.0, 66.0	5.0, 63.0
Change from baseline		
n	35	10
Mean (SD)	2.51 (9.27)	1.02 (14.03)
SE	1.57	4.44
Median	2.00	0.00
Min, Max	-20.0, 25.0	-24.0, 29.0

mNIS+7 score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurologic impairment (range = 0 to 304). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Alnylam Pharmaceuticals Inc.
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Table 2.8
Modified Neuropathy Impairment Score +7 (mNIS+7) Components: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Component: Quantitative Sensory Testing (QST)

FAP Stage: II&III

Subgroup Visit	Vutrisiran (HELIOS-A) (N=38)	Patisiran (HELIOS-A) (N=11)
Month 18		
Actual Value		
n	34	8
Mean (SD)	27.74 (17.50)	23.51 (10.60)
SE	3.00	3.75
Median	23.00	22.00
Min, Max	2.0, 78.0	6.1, 39.0
Change from baseline		
n	34	8
Mean (SD)	2.24 (11.38)	-4.21 (8.03)
SE	1.95	2.84
Median	0.00	-2.50
Min, Max	-22.0, 37.0	-18.0, 5.0

mNIS+7 score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurologic impairment (range = 0 to 304). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

Alnylam Pharmaceuticals Inc.
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Table 2.8
Modified Neuropathy Impairment Score +7 (mNIS+7) Components: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Component: Quantitative Sensory Testing (QST)

Cardiac Subpopulation: Yes

Subgroup Visit	Vutrisiran (HELIOS-A) (N=40)	Patisiran (HELIOS-A) (N=14)
Baseline		
n	40	14
Mean (SD)	22.13 (15.19)	16.77 (10.38)
SE	2.40	2.78
Median	20.00	15.50
Min, Max	0.0, 50.0	6.0, 42.0
Month 9		
Actual Value		
n	38	14
Mean (SD)	24.71 (18.69)	18.14 (17.46)
SE	3.03	4.67
Median	21.00	17.00
Min, Max	0.0, 66.0	0.0, 63.0
Change from baseline		
n	38	14
Mean (SD)	2.45 (9.52)	1.37 (11.13)
SE	1.54	2.98
Median	2.00	-2.00
Min, Max	-28.0, 25.0	-10.8, 29.0

mNIS+7 score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurologic impairment (range = 0 to 304). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 2.8
Modified Neuropathy Impairment Score +7 (mNIS+7) Components: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Component: Quantitative Sensory Testing (QST)

Cardiac Subpopulation: Yes

Subgroup Visit	Vutrisiran (HELIOS-A) (N=40)	Patisiran (HELIOS-A) (N=14)
Month 18		
Actual Value		
n	37	13
Mean (SD)	25.92 (20.84)	19.39 (12.51)
SE	3.43	3.47
Median	24.00	16.00
Min, Max	0.0, 78.0	6.0, 40.0
Change from baseline		
n	37	13
Mean (SD)	3.43 (12.43)	2.95 (10.68)
SE	2.04	2.96
Median	2.00	2.00
Min, Max	-26.0, 37.0	-11.7, 28.0

mNIS+7 score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurologic impairment (range = 0 to 304). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 2.8
Modified Neuropathy Impairment Score +7 (mNIS+7) Components: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Component: Quantitative Sensory Testing (QST)

Cardiac Subpopulation: No

Subgroup Visit	Vutrisiran (HELIOS-A) (N=82)	Patisiran (HELIOS-A) (N=28)
Baseline		
n	82	28
Mean (SD)	23.43 (18.56)	21.07 (15.92)
SE	2.05	3.01
Median	20.00	17.50
Min, Max	0.0, 74.0	0.0, 49.0
Month 9		
Actual Value		
n	79	26
Mean (SD)	20.08 (19.03)	17.96 (15.24)
SE	2.14	2.99
Median	16.00	14.00
Min, Max	0.0, 68.0	0.0, 49.0
Change from baseline		
n	79	26
Mean (SD)	-2.92 (11.32)	-1.27 (10.49)
SE	1.27	2.06
Median	-1.00	-0.50
Min, Max	-29.0, 36.0	-33.0, 16.0

mNIS+7 score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurologic impairment (range = 0 to 304). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 2.8
Modified Neuropathy Impairment Score +7 (mNIS+7) Components: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Component: Quantitative Sensory Testing (QST)

Cardiac Subpopulation: No

Subgroup Visit	Vutrisiran (HELIOS-A) (N=82)	Patisiran (HELIOS-A) (N=28)
Month 18		
Actual Value		
n	78	25
Mean (SD)	19.64 (18.38)	16.75 (14.99)
SE	2.08	3.00
Median	14.50	15.00
Min, Max	0.0, 66.0	0.0, 52.0
Change from baseline		
n	78	25
Mean (SD)	-3.50 (9.72)	-3.25 (8.86)
SE	1.10	1.77
Median	-2.00	-1.13
Min, Max	-33.0, 20.0	-34.0, 8.0

mNIS+7 score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurologic impairment (range = 0 to 304). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 2.8
Modified Neuropathy Impairment Score +7 (mNIS+7) Components: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Component: Quantitative Sensory Testing (QST)

Weight (kg): <65

Subgroup Visit	Vutrisiran (HELIOS-A) (N=46)	Patisiran (HELIOS-A) (N=15)
Baseline		
n	46	15
Mean (SD)	26.72 (17.36)	20.73 (15.63)
SE	2.56	4.03
Median	23.50	16.00
Min, Max	0.0, 74.0	0.0, 48.0
Month 9		
Actual Value		
n	44	15
Mean (SD)	25.50 (18.36)	22.87 (16.50)
SE	2.77	4.26
Median	20.00	19.00
Min, Max	0.0, 68.0	0.0, 49.0
Change from baseline		
n	44	15
Mean (SD)	-1.55 (11.18)	2.13 (7.87)
SE	1.69	2.03
Median	0.00	1.00
Min, Max	-29.0, 36.0	-7.0, 20.0

mNIS+7 score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurologic impairment (range = 0 to 304). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 2.8
Modified Neuropathy Impairment Score +7 (mNIS+7) Components: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Component: Quantitative Sensory Testing (QST)

Weight (kg): <65

Subgroup Visit	Vutrisiran (HELIOS-A) (N=46)	Patisiran (HELIOS-A) (N=15)
Month 18		
Actual Value		
n	42	15
Mean (SD)	26.62 (17.94)	21.79 (16.58)
SE	2.77	4.28
Median	23.00	15.00
Min, Max	0.0, 66.0	0.0, 52.0
Change from baseline		
n	42	15
Mean (SD)	0.38 (8.99)	1.06 (9.12)
SE	1.39	2.35
Median	0.00	-1.00
Min, Max	-26.0, 20.0	-11.0, 28.0

mNIS+7 score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurologic impairment (range = 0 to 304). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 2.8
Modified Neuropathy Impairment Score +7 (mNIS+7) Components: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Component: Quantitative Sensory Testing (QST)

Weight (kg): ≥65

Subgroup Visit	Vutrisiran (HELIOS-A) (N=76)	Patisiran (HELIOS-A) (N=27)
Baseline		
n	76	27
Mean (SD)	20.75 (17.27)	19.03 (13.83)
SE	1.98	2.66
Median	17.50	17.78
Min, Max	0.0, 72.0	0.0, 49.0
Month 9		
Actual Value		
n	73	25
Mean (SD)	19.22 (19.06)	15.12 (14.99)
SE	2.23	3.00
Median	13.00	14.00
Min, Max	0.0, 66.0	0.0, 63.0
Change from baseline		
n	73	25
Mean (SD)	-0.96 (10.99)	-1.83 (11.92)
SE	1.29	2.38
Median	0.00	-2.00
Min, Max	-28.1, 25.0	-33.0, 29.0

mNIS+7 score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurologic impairment (range = 0 to 304). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 2.8
Modified Neuropathy Impairment Score +7 (mNIS+7) Components: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Component: Quantitative Sensory Testing (QST)

Weight (kg): ≥65

Subgroup Visit	Vutrisiran (HELIOS-A) (N=76)	Patisiran (HELIOS-A) (N=27)
Month 18		
Actual Value		
n	73	23
Mean (SD)	18.81 (19.65)	14.96 (11.78)
SE	2.30	2.46
Median	11.00	16.00
Min, Max	0.0, 78.0	0.0, 42.0
Change from baseline		
n	73	23
Mean (SD)	-2.22 (12.11)	-2.55 (10.22)
SE	1.42	2.13
Median	-2.00	-2.00
Min, Max	-33.0, 37.0	-34.0, 19.0

mNIS+7 score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurologic impairment (range = 0 to 304). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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mNIS+7 – Domäne Σ5 *Nerve Conduction Studies*

Alnylam Pharmaceuticals Inc.
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Table 2.6
Modified Neuropathy Impairment Score +7 (mNIS+7) Component Scores: Change from Baseline to Month 18, MMRM Model
Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A) Subgroup Analysis
mITT Population

Nerve Conduction Study (NCS)

Subgroup Visit	LS Mean (95% CI) Vutrisiran (HELIOS-A) (N=122)	LS Mean (95% CI) Patisiran (HELIOS-A) (N=42)	LS Mean Difference (Vutrisiran-Patisiran) (95% CI), p-value	Standardized Effect Size (95% CI)
Age (years)				
<65	75	30		
Month 9	0.16 (-0.02, 0.34)	0.34 (0.05, 0.62)	-0.18 (-0.52, 0.16), 0.2944	-0.24 (-0.66, 0.19)
Month 18	0.12 (-0.11, 0.34)	0.42 (0.06, 0.79)	-0.31 (-0.73, 0.12), 0.1601	-0.28 (-0.71, 0.14)
≥65	44	10		
Month 9	-0.02 (-0.25, 0.22)	0.34 (-0.15, 0.82)	-0.35 (-0.89, 0.18), 0.1977	-0.40 (-1.08, 0.28)
Month 18	-0.06 (-0.32, 0.21)	0.42 (-0.11, 0.96)	-0.48 (-1.07, 0.12), 0.1182	-0.44 (-1.16, 0.27)
p-value of Treatment*Age	0.5870			

mNIS+7 score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurologic impairment (range = 0 to 304). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.
LS estimates and p-value derived from mixed-effects model for repeated measures (MMRM), controlling for categorical factors (treatment, visit), the subgroup variable, continuous covariate (baseline value), and interaction (treatment by visit, treatment by subgroup).
Standardized effect size (d) = LS mean difference/estimated pooled standard deviation with the small sample bias correction.

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Table 2.6
Modified Neuropathy Impairment Score +7 (mNIS+7) Component Scores: Change from Baseline to Month 18, MMRM Model
Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A) Subgroup Analysis
mITT Population

Nerve Conduction Study (NCS)

Subgroup Visit	LS Mean (95% CI) Vutrisiran (HELIOS-A) (N=122)	LS Mean (95% CI) Patisiran (HELIOS-A) (N=42)	LS Mean Difference (Vutrisiran-Patisiran) (95% CI), p-value	Standardized Effect Size (95% CI)
Sex				
Male	77	25		
Month 9	0.13 (-0.05, 0.30)	0.22 (-0.09, 0.53)	-0.10 (-0.45, 0.26), 0.5992	-0.11 (-0.56, 0.34)
Month 18	0.09 (-0.13, 0.31)	0.30 (-0.08, 0.69)	-0.22 (-0.66, 0.23), 0.3389	-0.22 (-0.68, 0.25)
Female	42	15		
Month 9	0.03 (-0.21, 0.27)	0.53 (0.13, 0.92)	-0.49 (-0.95, -0.03), 0.0356	-0.72 (-1.32, -0.13)
Month 18	-0.01 (-0.28, 0.27)	0.61 (0.15, 1.06)	-0.62 (-1.14, -0.09), 0.0226	-0.51 (-1.10, 0.08)
p-value of Treatment*Sex	0.1675			

mNIS+7 score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurologic impairment (range = 0 to 304). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.
LS estimates and p-value derived from mixed-effects model for repeated measures (MMRM), controlling for categorical factors (treatment, visit), the subgroup variable, continuous covariate (baseline value), and interaction (treatment by visit, treatment by subgroup).
Standardized effect size (d) = LS mean difference/estimated pooled standard deviation with the small sample bias correction.

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Table 2.6
Modified Neuropathy Impairment Score +7 (mNIS+7) Component Scores: Change from Baseline to Month 18, MMRM Model
Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A) Subgroup Analysis
mITT Population

Nerve Conduction Study (NCS)

Subgroup Visit	LS Mean (95% CI) Vutrisiran (HELIOS-A) (N=122)	LS Mean (95% CI) Patisiran (HELIOS-A) (N=42)	LS Mean Difference (Vutrisiran-Patisiran) (95% CI), p-value	Standardized Effect Size (95% CI)
Race				
White	84	28		
Month 9	0.06 (-0.11, 0.23)	0.32 (0.02, 0.62)	-0.26 (-0.60, 0.09), 0.1420	-0.29 (-0.72, 0.13)
Month 18	0.02 (-0.19, 0.24)	0.40 (0.03, 0.78)	-0.38 (-0.81, 0.05), 0.0823	-0.35 (-0.79, 0.08)
All Other Races	35	12		
Month 9	0.17 (-0.09, 0.43)	0.38 (-0.07, 0.82)	-0.21 (-0.72, 0.31), 0.4298	-0.34 (-0.99, 0.31)
Month 18	0.13 (-0.16, 0.42)	0.46 (-0.04, 0.96)	-0.33 (-0.91, 0.25), 0.2603	-0.31 (-0.99, 0.36)
p-value of Treatment*Race	0.8721			

mNIS+7 score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurologic impairment (range = 0 to 304). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.
LS estimates and p-value derived from mixed-effects model for repeated measures (MMRM), controlling for categorical factors (treatment, visit), the subgroup variable, continuous covariate (baseline value), and interaction (treatment by visit, treatment by subgroup).
Standardized effect size (d) = LS mean difference/estimated pooled standard deviation with the small sample bias correction.

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Table 2.6
Modified Neuropathy Impairment Score +7 (mNIS+7) Component Scores: Change from Baseline to Month 18, MMRM Model
Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A) Subgroup Analysis
mITT Population

Nerve Conduction Study (NCS)

Subgroup Visit	LS Mean (95% CI) Vutrisiran (HELIOS-A) (N=122)	LS Mean (95% CI) Patisiran (HELIOS-A) (N=42)	LS Mean Difference (Vutrisiran-Patisiran) (95% CI), p-value	Standardized Effect Size (95% CI)
Region				
North America	27	8		
Month 9	-0.09 (-0.41, 0.22)	-0.00 (-0.55, 0.54)	-0.09 (-0.71, 0.53), 0.7684	-0.08 (-0.86, 0.69)
Month 18	-0.13 (-0.47, 0.21)	0.08 (-0.51, 0.67)	-0.21 (-0.88, 0.46), 0.5309	-0.15 (-0.96, 0.67)
Western Europe	40	18		
Month 9	0.11 (-0.13, 0.36)	0.42 (0.05, 0.79)	-0.31 (-0.75, 0.13), 0.1665	-0.41 (-0.97, 0.14)
Month 18	0.07 (-0.20, 0.35)	0.50 (0.08, 0.93)	-0.43 (-0.93, 0.07), 0.0934	-0.48 (-1.04, 0.07)
Rest of World	52	14		
Month 9	0.17 (-0.05, 0.39)	0.42 (0.01, 0.83)	-0.25 (-0.72, 0.21), 0.2849	-0.37 (-0.96, 0.22)
Month 18	0.13 (-0.12, 0.38)	0.50 (0.04, 0.97)	-0.37 (-0.90, 0.16), 0.1663	-0.38 (-0.99, 0.22)
p-value of Treatment*Region	0.8467			

mNIS+7 score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurologic impairment (range = 0 to 304). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.
LS estimates and p-value derived from mixed-effects model for repeated measures (MMRM), controlling for categorical factors (treatment, visit), the subgroup variable, continuous covariate (baseline value), and interaction (treatment by visit, treatment by subgroup).
Standardized effect size (d) = LS mean difference/estimated pooled standard deviation with the small sample bias correction.

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Table 2.6
Modified Neuropathy Impairment Score +7 (mNIS+7) Component Scores: Change from Baseline to Month 18, MMRM Model
Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A) Subgroup Analysis
mITT Population

Nerve Conduction Study (NCS)

Subgroup Visit	LS Mean (95% CI) Vutrisiran (HELIOS-A) (N=122)	LS Mean (95% CI) Patisiran (HELIOS-A) (N=42)	LS Mean Difference (Vutrisiran-Patisiran) (95% CI), p-value	Standardized Effect Size (95% CI)
Baseline NIS				
<50	77	27		
Month 9	0.07 (-0.12, 0.27)	0.34 (0.04, 0.65)	-0.27 (-0.62, 0.08), 0.1328	-0.29 (-0.73, 0.14)
Month 18	0.04 (-0.20, 0.27)	0.43 (0.05, 0.81)	-0.39 (-0.83, 0.05), 0.0791	-0.33 (-0.78, 0.11)
≥50	42	13		
Month 9	0.13 (-0.14, 0.40)	0.32 (-0.11, 0.76)	-0.19 (-0.68, 0.30), 0.4348	-0.36 (-0.98, 0.26)
Month 18	0.09 (-0.21, 0.38)	0.41 (-0.09, 0.90)	-0.32 (-0.88, 0.24), 0.2601	-0.37 (-1.01, 0.26)
p-value of Treatment*Baseline NIS	0.8045			

mNIS+7 score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurologic impairment (range = 0 to 304). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.
LS estimates and p-value derived from mixed-effects model for repeated measures (MMRM), controlling for categorical factors (treatment, visit), the subgroup variable, continuous covariate (baseline value), and interaction (treatment by visit, treatment by subgroup).
Standardized effect size (d) = LS mean difference/estimated pooled standard deviation with the small sample bias correction.

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Table 2.6
Modified Neuropathy Impairment Score +7 (mNIS+7) Component Scores: Change from Baseline to Month 18, MMRM Model
Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A) Subgroup Analysis
mITT Population

Nerve Conduction Study (NCS)

Subgroup Visit	LS Mean (95% CI) Vutrisiran (HELIOS-A) (N=122)	LS Mean (95% CI) Patisiran (HELIOS-A) (N=42)	LS Mean Difference (Vutrisiran-Patisiran) (95% CI), p-value	Standardized Effect Size (95% CI)
Previous Tetramer Stabilizer Use				
Yes	74	32		
Month 9	0.09 (-0.09, 0.27)	0.44 (0.16, 0.71)	-0.35 (-0.68, -0.02), 0.0389	-0.48 (-0.90, -0.06)
Month 18	0.05 (-0.18, 0.27)	0.52 (0.16, 0.88)	-0.47 (-0.89, -0.05), 0.0293	-0.41 (-0.84, 0.01)
No	45	8		
Month 9	0.10 (-0.14, 0.34)	-0.07 (-0.60, 0.47)	0.17 (-0.42, 0.75), 0.5725	0.18 (-0.57, 0.92)
Month 18	0.06 (-0.21, 0.33)	0.02 (-0.57, 0.60)	0.05 (-0.60, 0.69), 0.8890	0.05 (-0.74, 0.83)
p-value of Treatment*Previous Tetramer Stabilizer Use	0.1240			

mNIS+7 score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurologic impairment (range = 0 to 304). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.
LS estimates and p-value derived from mixed-effects model for repeated measures (MMRM), controlling for categorical factors (treatment, visit), the subgroup variable, continuous covariate (baseline value), and interaction (treatment by visit, treatment by subgroup).
Standardized effect size (d) = LS mean difference/estimated pooled standard deviation with the small sample bias correction.

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Table 2.6
Modified Neuropathy Impairment Score +7 (mNIS+7) Component Scores: Change from Baseline to Month 18, MMRM Model
Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A) Subgroup Analysis
mITT Population

Nerve Conduction Study (NCS)

Subgroup Visit	LS Mean (95% CI) Vutrisiran (HELIOS-A) (N=122)	LS Mean (95% CI) Patisiran (HELIOS-A) (N=42)	LS Mean Difference (Vutrisiran-Patisiran) (95% CI), p-value	Standardized Effect Size (95% CI)
Genotype				
V30M	53	20		
Month 9	0.17 (-0.04, 0.39)	0.49 (0.15, 0.84)	-0.32 (-0.72, 0.08), 0.1212	-0.43 (-0.95, 0.08)
Month 18	0.14 (-0.11, 0.38)	0.57 (0.16, 0.99)	-0.44 (-0.92, 0.04), 0.0743	-0.50 (-1.02, 0.02)
non-V30M	66	20		
Month 9	0.03 (-0.16, 0.22)	0.18 (-0.16, 0.52)	-0.15 (-0.54, 0.24), 0.4434	-0.18 (-0.68, 0.32)
Month 18	-0.01 (-0.25, 0.22)	0.26 (-0.16, 0.68)	-0.27 (-0.75, 0.21), 0.2609	-0.22 (-0.74, 0.30)
p-value of Treatment*Genotype	0.5528			

mNIS+7 score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurologic impairment (range = 0 to 304). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.
LS estimates and p-value derived from mixed-effects model for repeated measures (MMRM), controlling for categorical factors (treatment, visit), the subgroup variable, continuous covariate (baseline value), and interaction (treatment by visit, treatment by subgroup).
Standardized effect size (d) = LS mean difference/estimated pooled standard deviation with the small sample bias correction.

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

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Table 2.6
Modified Neuropathy Impairment Score +7 (mNIS+7) Component Scores: Change from Baseline to Month 18, MMRM Model
Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A) Subgroup Analysis
mITT Population

Nerve Conduction Study (NCS)

Subgroup Visit	LS Mean (95% CI) Vutrisiran (HELIOS-A) (N=122)	LS Mean (95% CI) Patisiran (HELIOS-A) (N=42)	LS Mean Difference (Vutrisiran-Patisiran) (95% CI), p-value	Standardized Effect Size (95% CI)
FAP Stage				
I	83	30		
Month 9	0.11 (-0.06, 0.28)	0.43 (0.15, 0.72)	-0.32 (-0.65, 0.01), 0.0565	-0.37 (-0.79, 0.05)
Month 18	0.07 (-0.15, 0.29)	0.51 (0.15, 0.88)	-0.44 (-0.87, -0.02), 0.0412	-0.37 (-0.79, 0.05)
II&III	36	10		
Month 9	0.06 (-0.20, 0.32)	0.05 (-0.44, 0.53)	0.01 (-0.53, 0.56), 0.9617	0.02 (-0.67, 0.71)
Month 18	0.02 (-0.28, 0.31)	0.12 (-0.42, 0.67)	-0.11 (-0.72, 0.51), 0.7351	-0.17 (-0.92, 0.59)
p-value of Treatment*FAP Stage	0.2908			

mNIS+7 score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurologic impairment (range = 0 to 304). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.
LS estimates and p-value derived from mixed-effects model for repeated measures (MMRM), controlling for categorical factors (treatment, visit), the subgroup variable, continuous covariate (baseline value), and interaction (treatment by visit, treatment by subgroup).
Standardized effect size (d) = LS mean difference/estimated pooled standard deviation with the small sample bias correction.

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Table 2.6
Modified Neuropathy Impairment Score +7 (mNIS+7) Component Scores: Change from Baseline to Month 18, MMRM Model
Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A) Subgroup Analysis
mITT Population

Nerve Conduction Study (NCS)

Subgroup Visit	LS Mean (95% CI) Vutrisiran (HELIOS-A) (N=122)	LS Mean (95% CI) Patisiran (HELIOS-A) (N=42)	LS Mean Difference (Vutrisiran-Patisiran) (95% CI), p-value	Standardized Effect Size (95% CI)
Cardiac Subpopulation				
Yes	38	14		
Month 9	0.22 (-0.04, 0.47)	0.23 (-0.18, 0.64)	-0.01 (-0.49, 0.47), 0.9609	-0.02 (-0.62, 0.59)
Month 18	0.18 (-0.11, 0.46)	0.31 (-0.16, 0.78)	-0.14 (-0.68, 0.41), 0.6273	-0.13 (-0.75, 0.49)
No	81	26		
Month 9	0.03 (-0.14, 0.21)	0.39 (0.09, 0.70)	-0.36 (-0.71, -0.01), 0.0441	-0.42 (-0.86, 0.02)
Month 18	-0.00 (-0.22, 0.22)	0.48 (0.10, 0.86)	-0.48 (-0.92, -0.04), 0.0315	-0.44 (-0.89, 0.01)
p-value of Treatment*Cardiac Subpopulation	0.2371			

mNIS+7 score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurologic impairment (range = 0 to 304). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.
LS estimates and p-value derived from mixed-effects model for repeated measures (MMRM), controlling for categorical factors (treatment, visit), the subgroup variable, continuous covariate (baseline value), and interaction (treatment by visit, treatment by subgroup).
Standardized effect size (d) = LS mean difference/estimated pooled standard deviation with the small sample bias correction.

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Table 2.6
Modified Neuropathy Impairment Score +7 (mNIS+7) Component Scores: Change from Baseline to Month 18, MMRM Model
Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A) Subgroup Analysis
mITT Population

Nerve Conduction Study (NCS)

Subgroup Visit	LS Mean (95% CI) Vutrisiran (HELIOS-A) (N=122)	LS Mean (95% CI) Patisiran (HELIOS-A) (N=42)	LS Mean Difference (Vutrisiran-Patisiran) (95% CI), p-value	Standardized Effect Size (95% CI)
Weight (kg)				
<65	44	15		
Month 9	0.21 (-0.03, 0.45)	0.53 (0.14, 0.92)	-0.32 (-0.78, 0.14), 0.1689	-0.49 (-1.08, 0.09)
Month 18	0.17 (-0.10, 0.44)	0.61 (0.16, 1.07)	-0.44 (-0.97, 0.09), 0.1006	-0.41 (-0.99, 0.18)
≥65	75	25		
Month 9	0.02 (-0.16, 0.21)	0.22 (-0.09, 0.53)	-0.20 (-0.56, 0.16), 0.2834	-0.22 (-0.68, 0.23)
Month 18	-0.02 (-0.24, 0.21)	0.30 (-0.09, 0.69)	-0.32 (-0.77, 0.13), 0.1646	-0.30 (-0.76, 0.17)
p-value of Treatment*Weight	0.6673			

mNIS+7 score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurologic impairment (range = 0 to 304). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.
LS estimates and p-value derived from mixed-effects model for repeated measures (MMRM), controlling for categorical factors (treatment, visit), the subgroup variable, continuous covariate (baseline value), and interaction (treatment by visit, treatment by subgroup).
Standardized effect size (d) = LS mean difference/estimated pooled standard deviation with the small sample bias correction.

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Table 2.8
Modified Neuropathy Impairment Score +7 (mNIS+7) Components: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Component: Nerve Conduction Study (NCS)

Age (years): <65

Subgroup Visit	Vutrisiran (HELIOS-A) (N=76)	Patisiran (HELIOS-A) (N=31)
Baseline		
n	76	31
Mean (SD)	6.38 (3.64)	6.25 (3.62)
SE	0.42	0.65
Median	7.50	7.50
Min, Max	0.0, 10.0	0.0, 10.0
Month 9		
Actual Value		
n	74	30
Mean (SD)	6.43 (3.70)	6.48 (3.53)
SE	0.43	0.64
Median	8.00	8.00
Min, Max	0.0, 10.0	0.0, 10.0
Change from baseline		
n	74	30
Mean (SD)	0.13 (0.72)	0.31 (0.84)
SE	0.08	0.15
Median	0.00	0.25
Min, Max	-1.5, 1.5	-1.2, 3.0

mNIS+7 score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurologic impairment (range = 0 to 304). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 2.8
Modified Neuropathy Impairment Score +7 (mNIS+7) Components: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Component: Nerve Conduction Study (NCS)

Age (years): <65

Subgroup Visit	Vutrisiran (HELIOS-A) (N=76)	Patisiran (HELIOS-A) (N=31)
Month 18		
Actual Value		
n	74	29
Mean (SD)	6.44 (3.66)	6.52 (3.45)
SE	0.43	0.64
Median	7.25	7.50
Min, Max	0.0, 10.0	0.0, 10.0
Change from baseline		
n	74	29
Mean (SD)	0.14 (0.93)	0.48 (1.41)
SE	0.11	0.26
Median	0.00	0.00
Min, Max	-2.5, 3.5	-3.0, 5.0

mNIS+7 score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurologic impairment (range = 0 to 304). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 2.8
Modified Neuropathy Impairment Score +7 (mNIS+7) Components: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Component: Nerve Conduction Study (NCS)

Age (years): ≥65

Subgroup Visit	Vutrisiran (HELIOS-A) (N=46)	Patisiran (HELIOS-A) (N=11)
Baseline		
n	46	11
Mean (SD)	5.33 (3.09)	5.91 (2.33)
SE	0.46	0.70
Median	5.00	6.00
Min, Max	0.0, 10.0	1.0, 9.0
Month 9		
Actual Value		
n	43	10
Mean (SD)	5.30 (2.94)	6.20 (2.34)
SE	0.45	0.74
Median	5.50	7.00
Min, Max	0.0, 9.0	1.5, 9.0
Change from baseline		
n	43	10
Mean (SD)	0.05 (0.96)	0.40 (0.66)
SE	0.15	0.21
Median	0.00	0.00
Min, Max	-2.5, 3.0	0.0, 2.0

mNIS+7 score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurologic impairment (range = 0 to 304). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

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Table 2.8
Modified Neuropathy Impairment Score +7 (mNIS+7) Components: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Component: Nerve Conduction Study (NCS)

Age (years): ≥65

Subgroup Visit	Vutrisiran (HELIOS-A) (N=46)	Patisiran (HELIOS-A) (N=11)
Month 18		
Actual Value		
n	41	9
Mean (SD)	5.14 (3.27)	6.28 (2.51)
SE	0.51	0.84
Median	6.00	6.00
Min, Max	0.0, 9.0	1.0, 9.0
Change from baseline		
n	41	9
Mean (SD)	-0.10 (1.15)	0.28 (0.62)
SE	0.18	0.21
Median	0.00	0.00
Min, Max	-4.0, 2.0	-0.5, 1.5

mNIS+7 score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurologic impairment (range = 0 to 304). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 2.8
Modified Neuropathy Impairment Score +7 (mNIS+7) Components: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Component: Nerve Conduction Study (NCS)

Sex: Male

Subgroup Visit	Vutrisiran (HELIOS-A) (N=79)	Patisiran (HELIOS-A) (N=27)
Baseline		
n	79	27
Mean (SD)	6.35 (3.39)	6.69 (2.75)
SE	0.38	0.53
Median	7.50	7.00
Min, Max	0.0, 10.0	0.5, 10.0
Month 9		
Actual Value		
n	76	25
Mean (SD)	6.43 (3.44)	6.80 (2.77)
SE	0.40	0.55
Median	7.50	7.50
Min, Max	0.0, 10.0	1.0, 10.0
Change from baseline		
n	76	25
Mean (SD)	0.11 (0.89)	0.19 (0.76)
SE	0.10	0.15
Median	0.00	0.00
Min, Max	-2.5, 3.0	-1.2, 2.0

mNIS+7 score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurologic impairment (range = 0 to 304). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 2.8
Modified Neuropathy Impairment Score +7 (mNIS+7) Components: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Component: Nerve Conduction Study (NCS)

Sex: Male

Subgroup Visit	Vutrisiran (HELIOS-A) (N=79)	Patisiran (HELIOS-A) (N=27)
Month 18		
Actual Value		
n	74	23
Mean (SD)	6.39 (3.54)	6.87 (2.78)
SE	0.41	0.58
Median	7.00	7.50
Min, Max	0.0, 10.0	1.0, 10.0
Change from baseline		
n	74	23
Mean (SD)	0.08 (1.04)	0.30 (0.86)
SE	0.12	0.18
Median	0.00	0.00
Min, Max	-4.0, 3.5	-1.2, 2.5

mNIS+7 score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurologic impairment (range = 0 to 304). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 2.8
Modified Neuropathy Impairment Score +7 (mNIS+7) Components: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Component: Nerve Conduction Study (NCS)

Sex: Female

Subgroup Visit	Vutrisiran (HELIOS-A) (N=43)	Patisiran (HELIOS-A) (N=15)
Baseline		
n	43	15
Mean (SD)	5.31 (3.55)	5.20 (4.06)
SE	0.54	1.05
Median	5.00	5.00
Min, Max	0.0, 10.0	0.0, 10.0
Month 9		
Actual Value		
n	41	15
Mean (SD)	5.23 (3.43)	5.77 (3.93)
SE	0.54	1.02
Median	5.00	8.00
Min, Max	0.0, 10.0	0.0, 10.0
Change from baseline		
n	41	15
Mean (SD)	0.08 (0.66)	0.57 (0.82)
SE	0.10	0.21
Median	0.00	0.50
Min, Max	-1.5, 1.5	0.0, 3.0

mNIS+7 score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurologic impairment (range = 0 to 304). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 2.8
Modified Neuropathy Impairment Score +7 (mNIS+7) Components: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Component: Nerve Conduction Study (NCS)

Sex: Female

Subgroup Visit	Vutrisiran (HELIOS-A) (N=43)	Patisiran (HELIOS-A) (N=15)
Month 18		
Actual Value		
n	41	15
Mean (SD)	5.22 (3.54)	5.83 (3.82)
SE	0.55	0.99
Median	6.00	6.00
Min, Max	0.0, 10.0	0.0, 10.0
Change from baseline		
n	41	15
Mean (SD)	0.02 (0.99)	0.63 (1.73)
SE	0.15	0.45
Median	0.00	0.00
Min, Max	-2.5, 2.5	-3.0, 5.0

mNIS+7 score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurologic impairment (range = 0 to 304). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 2.8
Modified Neuropathy Impairment Score +7 (mNIS+7) Components: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Component: Nerve Conduction Study (NCS)

Race: White

Subgroup Visit	Vutrisiran (HELIOS-A) (N=86)	Patisiran (HELIOS-A) (N=29)
Baseline		
n	86	29
Mean (SD)	5.97 (3.41)	6.82 (3.21)
SE	0.37	0.60
Median	6.75	8.00
Min, Max	0.0, 10.0	0.0, 10.0
Month 9		
Actual Value		
n	83	28
Mean (SD)	6.04 (3.52)	7.14 (3.10)
SE	0.39	0.59
Median	7.00	8.00
Min, Max	0.0, 10.0	0.0, 10.0
Change from baseline		
n	83	28
Mean (SD)	0.09 (0.90)	0.33 (0.79)
SE	0.10	0.15
Median	0.00	0.25
Min, Max	-2.5, 3.0	-1.2, 3.0

mNIS+7 score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurologic impairment (range = 0 to 304). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 2.8
Modified Neuropathy Impairment Score +7 (mNIS+7) Components: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Component: Nerve Conduction Study (NCS)

Race: White

Subgroup Visit	Vutrisiran (HELIOS-A) (N=86)	Patisiran (HELIOS-A) (N=29)
Month 18		
Actual Value		
n	82	27
Mean (SD)	5.90 (3.58)	6.93 (3.26)
SE	0.40	0.63
Median	7.00	8.00
Min, Max	0.0, 10.0	0.0, 10.0
Change from baseline		
n	82	27
Mean (SD)	-0.05 (1.09)	0.23 (1.01)
SE	0.12	0.19
Median	0.00	0.00
Min, Max	-4.0, 3.5	-3.0, 2.0

mNIS+7 score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurologic impairment (range = 0 to 304). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 2.8
Modified Neuropathy Impairment Score +7 (mNIS+7) Components: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Component: Nerve Conduction Study (NCS)

Race: All Other Races

Subgroup Visit	Vutrisiran (HELIOS-A) (N=36)	Patisiran (HELIOS-A) (N=13)
Baseline		
n	36	13
Mean (SD)	6.03 (3.66)	4.69 (3.15)
SE	0.61	0.87
Median	7.00	4.00
Min, Max	0.0, 10.0	0.5, 10.0
Month 9		
Actual Value		
n	34	12
Mean (SD)	5.94 (3.40)	4.71 (3.03)
SE	0.58	0.88
Median	6.75	5.25
Min, Max	0.0, 10.0	1.0, 10.0
Change from baseline		
n	34	12
Mean (SD)	0.12 (0.56)	0.33 (0.83)
SE	0.10	0.24
Median	0.00	0.00
Min, Max	-1.0, 1.5	-1.0, 2.0

mNIS+7 score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurologic impairment (range = 0 to 304). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

Alnylam Pharmaceuticals Inc.
ALN-TTRSC02-002

Table 2.8
Modified Neuropathy Impairment Score +7 (mNIS+7) Components: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Component: Nerve Conduction Study (NCS)

Race: All Other Races

Subgroup Visit	Vutrisiran (HELIOS-A) (N=36)	Patisiran (HELIOS-A) (N=13)
Month 18		
Actual Value		
n	33	11
Mean (SD)	6.15 (3.58)	5.32 (2.96)
SE	0.62	0.89
Median	7.00	6.00
Min, Max	0.0, 10.0	1.0, 10.0
Change from baseline		
n	33	11
Mean (SD)	0.32 (0.76)	0.91 (1.70)
SE	0.13	0.51
Median	0.00	0.50
Min, Max	-1.0, 2.5	-1.0, 5.0

mNIS+7 score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurologic impairment (range = 0 to 304). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

Alnylam Pharmaceuticals Inc.
ALN-TTRSC02-002

Table 2.8
Modified Neuropathy Impairment Score +7 (mNIS+7) Components: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Component: Nerve Conduction Study (NCS)

Region: North America

Subgroup Visit	Vutrisiran (HELIOS-A) (N=27)	Patisiran (HELIOS-A) (N=8)
Baseline		
n	27	8
Mean (SD)	3.37 (3.03)	4.14 (3.11)
SE	0.58	1.10
Median	3.00	5.00
Min, Max	0.0, 10.0	0.0, 8.0
Month 9		
Actual Value		
n	25	8
Mean (SD)	3.13 (2.87)	4.38 (2.94)
SE	0.57	1.04
Median	2.50	4.50
Min, Max	0.0, 9.0	0.0, 8.5
Change from baseline		
n	25	8
Mean (SD)	0.21 (1.20)	0.23 (0.70)
SE	0.24	0.25
Median	0.00	0.25
Min, Max	-2.5, 3.0	-1.2, 1.0

mNIS+7 score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurologic impairment (range = 0 to 304). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

Alnylam Pharmaceuticals Inc.
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Table 2.8
Modified Neuropathy Impairment Score +7 (mNIS+7) Components: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Component: Nerve Conduction Study (NCS)

Region: North America

Subgroup Visit	Vutrisiran (HELIOS-A) (N=27)	Patisiran (HELIOS-A) (N=8)
Month 18		
Actual Value		
n	25	7
Mean (SD)	2.92 (3.14)	4.00 (2.43)
SE	0.63	0.92
Median	2.00	5.00
Min, Max	0.0, 10.0	0.0, 7.0
Change from baseline		
n	25	7
Mean (SD)	-0.30 (1.43)	-0.17 (1.56)
SE	0.29	0.59
Median	0.00	0.00
Min, Max	-4.0, 3.5	-3.0, 1.5

mNIS+7 score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurologic impairment (range = 0 to 304). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

Alnylam Pharmaceuticals Inc.
ALN-TTRSC02-002

Table 2.8
Modified Neuropathy Impairment Score +7 (mNIS+7) Components: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Component: Nerve Conduction Study (NCS)

Region: Western Europe

Subgroup Visit	Vutrisiran (HELIOS-A) (N=42)	Patisiran (HELIOS-A) (N=20)
Baseline		
n	42	20
Mean (SD)	6.39 (3.16)	7.20 (2.69)
SE	0.49	0.60
Median	7.00	8.00
Min, Max	0.0, 10.0	1.0, 10.0
Month 9		
Actual Value		
n	40	18
Mean (SD)	6.51 (3.12)	7.53 (2.61)
SE	0.49	0.62
Median	7.00	8.00
Min, Max	0.0, 10.0	1.5, 10.0
Change from baseline		
n	40	18
Mean (SD)	0.08 (0.73)	0.39 (0.88)
SE	0.12	0.21
Median	0.00	0.25
Min, Max	-1.5, 1.5	-1.0, 3.0

mNIS+7 score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurologic impairment (range = 0 to 304). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

Alnylam Pharmaceuticals Inc.
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Table 2.8
Modified Neuropathy Impairment Score +7 (mNIS+7) Components: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Component: Nerve Conduction Study (NCS)

Region: Western Europe

Subgroup Visit	Vutrisiran (HELIOS-A) (N=42)	Patisiran (HELIOS-A) (N=20)
Month 18		
Actual Value		
n	40	18
Mean (SD)	6.53 (3.17)	7.50 (2.95)
SE	0.50	0.69
Median	7.00	8.25
Min, Max	0.0, 10.0	0.0, 10.0
Change from baseline		
n	40	18
Mean (SD)	0.09 (0.94)	0.36 (0.76)
SE	0.15	0.18
Median	0.00	0.00
Min, Max	-2.0, 2.5	-1.0, 2.0

mNIS+7 score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurologic impairment (range = 0 to 304). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Alnylam Pharmaceuticals Inc.
ALN-TTRSC02-002

Table 2.8
Modified Neuropathy Impairment Score +7 (mNIS+7) Components: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Component: Nerve Conduction Study (NCS)

Region: Rest of World

Subgroup Visit	Vutrisiran (HELIOS-A) (N=53)	Patisiran (HELIOS-A) (N=14)
Baseline		
n	53	14
Mean (SD)	6.99 (3.28)	5.82 (3.80)
SE	0.45	1.02
Median	8.00	6.00
Min, Max	0.0, 10.0	0.5, 10.0
Month 9		
Actual Value		
n	52	14
Mean (SD)	7.02 (3.28)	6.14 (3.69)
SE	0.45	0.99
Median	8.00	7.00
Min, Max	0.0, 10.0	1.0, 10.0
Change from baseline		
n	52	14
Mean (SD)	0.07 (0.65)	0.32 (0.77)
SE	0.09	0.21
Median	0.00	0.00
Min, Max	-1.5, 1.5	-1.0, 2.0

mNIS+7 score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurologic impairment (range = 0 to 304). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

Alnylam Pharmaceuticals Inc.
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Table 2.8
Modified Neuropathy Impairment Score +7 (mNIS+7) Components: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Component: Nerve Conduction Study (NCS)

Region: Rest of World

Subgroup Visit	Vutrisiran (HELIOS-A) (N=53)	Patisiran (HELIOS-A) (N=14)
Month 18		
Actual Value		
n	50	13
Mean (SD)	7.06 (3.25)	6.35 (3.41)
SE	0.46	0.94
Median	8.00	6.00
Min, Max	0.0, 10.0	1.0, 10.0
Change from baseline		
n	50	13
Mean (SD)	0.21 (0.78)	0.85 (1.57)
SE	0.11	0.44
Median	0.00	0.50
Min, Max	-2.5, 2.5	-1.0, 5.0

mNIS+7 score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurologic impairment (range = 0 to 304). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Alnylam Pharmaceuticals Inc.
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Table 2.8
Modified Neuropathy Impairment Score +7 (mNIS+7) Components: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Component: Nerve Conduction Study (NCS)

Baseline NIS: <50

Subgroup Visit	Vutrisiran (HELIOS-A) (N=78)	Patisiran (HELIOS-A) (N=27)
Baseline		
n	78	27
Mean (SD)	4.46 (3.28)	5.10 (3.30)
SE	0.37	0.64
Median	4.50	6.00
Min, Max	0.0, 10.0	0.0, 10.0
Month 9		
Actual Value		
n	77	27
Mean (SD)	4.56 (3.33)	5.52 (3.28)
SE	0.38	0.63
Median	4.00	6.00
Min, Max	0.0, 10.0	0.0, 10.0
Change from baseline		
n	77	27
Mean (SD)	0.16 (0.93)	0.42 (0.84)
SE	0.11	0.16
Median	0.00	0.50
Min, Max	-2.5, 3.0	-1.2, 3.0

mNIS+7 score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurologic impairment (range = 0 to 304). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 2.8
Modified Neuropathy Impairment Score +7 (mNIS+7) Components: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Component: Nerve Conduction Study (NCS)

Baseline NIS: <50

Subgroup Visit	Vutrisiran (HELIOS-A) (N=78)	Patisiran (HELIOS-A) (N=27)
Month 18		
Actual Value		
n	75	26
Mean (SD)	4.45 (3.45)	5.52 (3.34)
SE	0.40	0.65
Median	4.50	6.00
Min, Max	0.0, 10.0	0.0, 10.0
Change from baseline		
n	75	26
Mean (SD)	0.07 (1.18)	0.38 (1.16)
SE	0.14	0.23
Median	0.00	0.00
Min, Max	-4.0, 3.5	-3.0, 2.5

mNIS+7 score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurologic impairment (range = 0 to 304). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Alnylam Pharmaceuticals Inc.
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Table 2.8
Modified Neuropathy Impairment Score +7 (mNIS+7) Components: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Component: Nerve Conduction Study (NCS)

Baseline NIS: ≥50

Subgroup Visit	Vutrisiran (HELIOS-A) (N=44)	Patisiran (HELIOS-A) (N=15)
Baseline		
n	44	15
Mean (SD)	8.69 (1.66)	8.07 (2.39)
SE	0.25	0.62
Median	9.25	8.50
Min, Max	5.0, 10.0	1.0, 10.0
Month 9		
Actual Value		
n	40	13
Mean (SD)	8.81 (1.41)	8.27 (2.31)
SE	0.22	0.64
Median	9.00	9.00
Min, Max	5.0, 10.0	1.5, 10.0
Change from baseline		
n	40	13
Mean (SD)	-0.03 (0.52)	0.15 (0.69)
SE	0.08	0.19
Median	0.00	0.00
Min, Max	-1.0, 1.5	-1.0, 2.0

mNIS+7 score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurologic impairment (range = 0 to 304). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 2.8
Modified Neuropathy Impairment Score +7 (mNIS+7) Components: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Component: Nerve Conduction Study (NCS)

Baseline NIS: ≥50

Subgroup Visit	Vutrisiran (HELIOS-A) (N=44)	Patisiran (HELIOS-A) (N=15)
Month 18		
Actual Value		
n	40	12
Mean (SD)	8.84 (1.32)	8.50 (1.72)
SE	0.21	0.50
Median	9.00	9.00
Min, Max	6.0, 10.0	5.0, 10.0
Change from baseline		
n	40	12
Mean (SD)	0.03 (0.61)	0.54 (1.51)
SE	0.10	0.44
Median	0.00	0.00
Min, Max	-1.0, 2.0	-1.0, 5.0

mNIS+7 score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurologic impairment (range = 0 to 304). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Alnylam Pharmaceuticals Inc.
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Table 2.8
Modified Neuropathy Impairment Score +7 (mNIS+7) Components: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Component: Nerve Conduction Study (NCS)

Previous Tetramer Stabilizer Use: Yes

Subgroup Visit	Vutrisiran (HELIOS-A) (N=75)	Patisiran (HELIOS-A) (N=33)
Baseline		
n	75	33
Mean (SD)	6.78 (3.28)	6.47 (3.33)
SE	0.38	0.58
Median	8.00	8.00
Min, Max	0.0, 10.0	0.5, 10.0
Month 9		
Actual Value		
n	74	32
Mean (SD)	6.86 (3.31)	6.81 (3.17)
SE	0.38	0.56
Median	8.00	8.00
Min, Max	0.0, 10.0	1.0, 10.0
Change from baseline		
n	74	32
Mean (SD)	0.05 (0.69)	0.41 (0.83)
SE	0.08	0.15
Median	0.00	0.50
Min, Max	-1.5, 2.0	-1.0, 3.0

mNIS+7 score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurologic impairment (range = 0 to 304). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Alnylam Pharmaceuticals Inc.
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Table 2.8
Modified Neuropathy Impairment Score +7 (mNIS+7) Components: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Component: Nerve Conduction Study (NCS)

Previous Tetramer Stabilizer Use: Yes

Subgroup Visit	Vutrisiran (HELIOS-A) (N=75)	Patisiran (HELIOS-A) (N=33)
Month 18		
Actual Value		
n	71	31
Mean (SD)	6.78 (3.43)	6.84 (3.10)
SE	0.41	0.56
Median	8.00	7.50
Min, Max	0.0, 10.0	0.0, 10.0
Change from baseline		
n	71	31
Mean (SD)	0.01 (1.04)	0.55 (1.36)
SE	0.12	0.24
Median	0.00	0.00
Min, Max	-4.0, 3.5	-3.0, 5.0

mNIS+7 score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurologic impairment (range = 0 to 304). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Alnylam Pharmaceuticals Inc.
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Table 2.8
Modified Neuropathy Impairment Score +7 (mNIS+7) Components: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Component: Nerve Conduction Study (NCS)

Previous Tetramer Stabilizer Use: No

Subgroup Visit	Vutrisiran (HELIOS-A) (N=47)	Patisiran (HELIOS-A) (N=9)
Baseline		
n	47	9
Mean (SD)	4.71 (3.41)	5.02 (3.13)
SE	0.50	1.04
Median	5.00	6.00
Min, Max	0.0, 10.0	0.0, 10.0
Month 9		
Actual Value		
n	43	8
Mean (SD)	4.56 (3.29)	4.81 (3.25)
SE	0.50	1.15
Median	5.00	5.00
Min, Max	0.0, 10.0	0.0, 10.0
Change from baseline		
n	43	8
Mean (SD)	0.18 (1.00)	0.04 (0.61)
SE	0.15	0.21
Median	0.00	0.00
Min, Max	-2.5, 3.0	-1.2, 1.0

mNIS+7 score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurologic impairment (range = 0 to 304). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 2.8
Modified Neuropathy Impairment Score +7 (mNIS+7) Components: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Component: Nerve Conduction Study (NCS)

Previous Tetramer Stabilizer Use: No

Subgroup Visit	Vutrisiran (HELIOS-A) (N=47)	Patisiran (HELIOS-A) (N=9)
Month 18		
Actual Value		
n	44	7
Mean (SD)	4.68 (3.45)	4.79 (3.44)
SE	0.52	1.30
Median	5.50	5.00
Min, Max	0.0, 10.0	0.0, 10.0
Change from baseline		
n	44	7
Mean (SD)	0.14 (0.98)	-0.09 (0.51)
SE	0.15	0.19
Median	0.00	0.00
Min, Max	-2.5, 2.0	-1.2, 0.5

mNIS+7 score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurologic impairment (range = 0 to 304). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 2.8
Modified Neuropathy Impairment Score +7 (mNIS+7) Components: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Component: Nerve Conduction Study (NCS)

Genotype: V30M

Subgroup Visit	Vutrisiran (HELIOS-A) (N=54)	Patisiran (HELIOS-A) (N=20)
Baseline		
n	54	20
Mean (SD)	6.47 (3.44)	7.15 (2.92)
SE	0.47	0.65
Median	7.50	8.00
Min, Max	0.0, 10.0	0.0, 10.0
Month 9		
Actual Value		
n	52	20
Mean (SD)	6.62 (3.33)	7.63 (2.72)
SE	0.46	0.61
Median	7.50	8.00
Min, Max	0.0, 10.0	0.0, 10.0
Change from baseline		
n	52	20
Mean (SD)	0.19 (0.68)	0.48 (0.95)
SE	0.09	0.21
Median	0.00	0.00
Min, Max	-1.0, 3.0	-1.0, 3.0

mNIS+7 score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurologic impairment (range = 0 to 304). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 2.8
Modified Neuropathy Impairment Score +7 (mNIS+7) Components: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Component: Nerve Conduction Study (NCS)

Genotype: V30M

Subgroup Visit	Vutrisiran (HELIOS-A) (N=54)	Patisiran (HELIOS-A) (N=20)
Month 18		
Actual Value		
n	52	20
Mean (SD)	6.47 (3.59)	7.55 (2.86)
SE	0.50	0.64
Median	7.25	8.25
Min, Max	0.0, 10.0	0.0, 10.0
Change from baseline		
n	52	20
Mean (SD)	0.02 (0.90)	0.40 (0.74)
SE	0.13	0.16
Median	0.00	0.00
Min, Max	-4.0, 2.0	-0.5, 2.0

mNIS+7 score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurologic impairment (range = 0 to 304). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 2.8
Modified Neuropathy Impairment Score +7 (mNIS+7) Components: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Component: Nerve Conduction Study (NCS)

Genotype: non-V30M

Subgroup Visit	Vutrisiran (HELIOS-A) (N=68)	Patisiran (HELIOS-A) (N=22)
Baseline		
n	68	22
Mean (SD)	5.60 (3.46)	5.26 (3.44)
SE	0.42	0.73
Median	6.00	6.08
Min, Max	0.0, 10.0	1.0, 10.0
Month 9		
Actual Value		
n	65	20
Mean (SD)	5.53 (3.53)	5.20 (3.33)
SE	0.44	0.75
Median	5.50	5.00
Min, Max	0.0, 10.0	1.0, 10.0
Change from baseline		
n	65	20
Mean (SD)	0.03 (0.91)	0.19 (0.59)
SE	0.11	0.13
Median	0.00	0.25
Min, Max	-2.5, 2.0	-1.2, 1.0

mNIS+7 score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurologic impairment (range = 0 to 304). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Alnylam Pharmaceuticals Inc.
ALN-TTRSC02-002

Table 2.8
Modified Neuropathy Impairment Score +7 (mNIS+7) Components: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Component: Nerve Conduction Study (NCS)

Genotype: non-V30M

Subgroup Visit	Vutrisiran (HELIOS-A) (N=68)	Patisiran (HELIOS-A) (N=22)
Month 18		
Actual Value		
n	63	18
Mean (SD)	5.56 (3.52)	5.25 (3.24)
SE	0.44	0.76
Median	6.00	5.00
Min, Max	0.0, 10.0	0.0, 10.0
Change from baseline		
n	63	18
Mean (SD)	0.09 (1.11)	0.46 (1.69)
SE	0.14	0.40
Median	0.00	0.00
Min, Max	-2.5, 3.5	-3.0, 5.0

mNIS+7 score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurologic impairment (range = 0 to 304). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

Alnylam Pharmaceuticals Inc.
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Table 2.8
Modified Neuropathy Impairment Score +7 (mNIS+7) Components: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Component: Nerve Conduction Study (NCS)

FAP Stage: I

Subgroup Visit	Vutrisiran (HELIOS-A) (N=84)	Patisiran (HELIOS-A) (N=31)
Baseline		
n	84	31
Mean (SD)	5.25 (3.56)	5.39 (3.38)
SE	0.39	0.61
Median	5.00	6.16
Min, Max	0.0, 10.0	0.0, 10.0
Month 9		
Actual Value		
n	82	30
Mean (SD)	5.31 (3.60)	5.80 (3.37)
SE	0.40	0.61
Median	5.75	7.00
Min, Max	0.0, 10.0	0.0, 10.0
Change from baseline		
n	82	30
Mean (SD)	0.17 (0.88)	0.46 (0.86)
SE	0.10	0.16
Median	0.00	0.50
Min, Max	-2.5, 3.0	-1.2, 3.0

mNIS+7 score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurologic impairment (range = 0 to 304). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

Alnylam Pharmaceuticals Inc.
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Table 2.8
Modified Neuropathy Impairment Score +7 (mNIS+7) Components: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Component: Nerve Conduction Study (NCS)

FAP Stage: I

Subgroup Visit	Vutrisiran (HELIOS-A) (N=84)	Patisiran (HELIOS-A) (N=31)
Month 18		
Actual Value		
n	81	30
Mean (SD)	5.17 (3.69)	5.87 (3.32)
SE	0.41	0.61
Median	6.00	6.00
Min, Max	0.0, 10.0	0.0, 10.0
Change from baseline		
n	81	30
Mean (SD)	0.03 (1.14)	0.53 (1.38)
SE	0.13	0.25
Median	0.00	0.00
Min, Max	-4.0, 3.5	-3.0, 5.0

mNIS+7 score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurologic impairment (range = 0 to 304). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

Alnylam Pharmaceuticals Inc.
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Table 2.8
Modified Neuropathy Impairment Score +7 (mNIS+7) Components: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Component: Nerve Conduction Study (NCS)

FAP Stage: II&III

Subgroup Visit	Vutrisiran (HELIOS-A) (N=38)	Patisiran (HELIOS-A) (N=11)
Baseline		
n	38	11
Mean (SD)	7.61 (2.63)	8.32 (1.91)
SE	0.43	0.58
Median	8.75	8.50
Min, Max	0.0, 10.0	4.0, 10.0
Month 9		
Actual Value		
n	35	10
Mean (SD)	7.66 (2.51)	8.25 (2.02)
SE	0.42	0.64
Median	8.50	8.50
Min, Max	1.0, 10.0	4.0, 10.0
Change from baseline		
n	35	10
Mean (SD)	-0.06 (0.62)	-0.05 (0.37)
SE	0.10	0.12
Median	0.00	0.00
Min, Max	-1.5, 1.5	-1.0, 0.5

mNIS+7 score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurologic impairment (range = 0 to 304). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Alnylam Pharmaceuticals Inc.
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Table 2.8
Modified Neuropathy Impairment Score +7 (mNIS+7) Components: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Component: Nerve Conduction Study (NCS)

FAP Stage: II&III

Subgroup Visit	Vutrisiran (HELIOS-A) (N=38)	Patisiran (HELIOS-A) (N=11)
Month 18		
Actual Value		
n	34	8
Mean (SD)	7.88 (2.37)	8.69 (1.44)
SE	0.41	0.51
Median	9.00	9.00
Min, Max	0.5, 10.0	6.0, 10.0
Change from baseline		
n	34	8
Mean (SD)	0.12 (0.66)	0.06 (0.56)
SE	0.11	0.20
Median	0.00	0.00
Min, Max	-1.0, 2.0	-1.0, 1.0

mNIS+7 score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurologic impairment (range = 0 to 304). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

Alnylam Pharmaceuticals Inc.
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Table 2.8
Modified Neuropathy Impairment Score +7 (mNIS+7) Components: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Component: Nerve Conduction Study (NCS)

Cardiac Subpopulation: Yes

Subgroup Visit	Vutrisiran (HELIOS-A) (N=40)	Patisiran (HELIOS-A) (N=14)
Baseline		
n	40	14
Mean (SD)	7.48 (2.71)	6.68 (3.30)
SE	0.43	0.88
Median	8.25	7.50
Min, Max	0.0, 10.0	1.0, 10.0
Month 9		
Actual Value		
n	38	14
Mean (SD)	7.61 (2.72)	6.75 (3.23)
SE	0.44	0.86
Median	8.50	7.25
Min, Max	0.0, 10.0	1.0, 10.0
Change from baseline		
n	38	14
Mean (SD)	0.13 (0.71)	0.07 (0.47)
SE	0.12	0.13
Median	0.00	0.00
Min, Max	-1.0, 1.5	-1.0, 1.0

mNIS+7 score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurologic impairment (range = 0 to 304). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Alnylam Pharmaceuticals Inc.
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Table 2.8
Modified Neuropathy Impairment Score +7 (mNIS+7) Components: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Component: Nerve Conduction Study (NCS)

Cardiac Subpopulation: Yes

Subgroup Visit	Vutrisiran (HELIOS-A) (N=40)	Patisiran (HELIOS-A) (N=14)
Month 18		
Actual Value		
n	37	13
Mean (SD)	7.55 (2.79)	7.12 (2.82)
SE	0.46	0.78
Median	8.50	7.50
Min, Max	0.0, 10.0	1.0, 10.0
Change from baseline		
n	37	13
Mean (SD)	0.15 (0.85)	0.69 (1.53)
SE	0.14	0.43
Median	0.00	0.00
Min, Max	-1.5, 2.0	-1.0, 5.0

mNIS+7 score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurologic impairment (range = 0 to 304). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 2.8
Modified Neuropathy Impairment Score +7 (mNIS+7) Components: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Component: Nerve Conduction Study (NCS)

Cardiac Subpopulation: No

Subgroup Visit	Vutrisiran (HELIOS-A) (N=82)	Patisiran (HELIOS-A) (N=28)
Baseline		
n	82	28
Mean (SD)	5.26 (3.57)	5.90 (3.34)
SE	0.39	0.63
Median	5.00	7.00
Min, Max	0.0, 10.0	0.0, 10.0
Month 9		
Actual Value		
n	79	26
Mean (SD)	5.25 (3.55)	6.23 (3.30)
SE	0.40	0.65
Median	5.00	7.75
Min, Max	0.0, 10.0	0.0, 10.0
Change from baseline		
n	79	26
Mean (SD)	0.08 (0.86)	0.47 (0.90)
SE	0.10	0.18
Median	0.00	0.50
Min, Max	-2.5, 3.0	-1.2, 3.0

mNIS+7 score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurologic impairment (range = 0 to 304). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 2.8
Modified Neuropathy Impairment Score +7 (mNIS+7) Components: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Component: Nerve Conduction Study (NCS)

Cardiac Subpopulation: No

Subgroup Visit	Vutrisiran (HELIOS-A) (N=82)	Patisiran (HELIOS-A) (N=28)
Month 18		
Actual Value		
n	78	25
Mean (SD)	5.23 (3.67)	6.12 (3.42)
SE	0.42	0.68
Median	5.75	6.50
Min, Max	0.0, 10.0	0.0, 10.0
Change from baseline		
n	78	25
Mean (SD)	0.01 (1.09)	0.29 (1.11)
SE	0.12	0.22
Median	0.00	0.00
Min, Max	-4.0, 3.5	-3.0, 2.0

mNIS+7 score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurologic impairment (range = 0 to 304). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 2.8
Modified Neuropathy Impairment Score +7 (mNIS+7) Components: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Component: Nerve Conduction Study (NCS)

Weight (kg): <65

Subgroup Visit	Vutrisiran (HELIOS-A) (N=46)	Patisiran (HELIOS-A) (N=15)
Baseline		
n	46	15
Mean (SD)	7.58 (2.61)	5.77 (3.77)
SE	0.38	0.97
Median	9.00	7.50
Min, Max	0.0, 10.0	0.0, 10.0
Month 9		
Actual Value		
n	44	15
Mean (SD)	7.68 (2.57)	6.37 (3.67)
SE	0.39	0.95
Median	8.50	8.00
Min, Max	0.0, 10.0	0.0, 10.0
Change from baseline		
n	44	15
Mean (SD)	0.10 (0.62)	0.60 (0.78)
SE	0.09	0.20
Median	0.00	0.50
Min, Max	-1.5, 1.5	0.0, 3.0

mNIS+7 score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurologic impairment (range = 0 to 304). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 2.8
Modified Neuropathy Impairment Score +7 (mNIS+7) Components: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Component: Nerve Conduction Study (NCS)

Weight (kg): <65

Subgroup Visit	Vutrisiran (HELIOS-A) (N=46)	Patisiran (HELIOS-A) (N=15)
Month 18		
Actual Value		
n	42	15
Mean (SD)	7.68 (2.52)	6.23 (3.58)
SE	0.39	0.92
Median	8.75	6.50
Min, Max	0.0, 10.0	0.0, 10.0
Change from baseline		
n	42	15
Mean (SD)	0.19 (0.83)	0.47 (1.68)
SE	0.13	0.43
Median	0.00	0.00
Min, Max	-2.5, 2.5	-3.0, 5.0

mNIS+7 score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurologic impairment (range = 0 to 304). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Alnylam Pharmaceuticals Inc.
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Table 2.8
Modified Neuropathy Impairment Score +7 (mNIS+7) Components: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Component: Nerve Conduction Study (NCS)

Weight (kg): ≥65

Subgroup Visit	Vutrisiran (HELIOS-A) (N=76)	Patisiran (HELIOS-A) (N=27)
Baseline		
n	76	27
Mean (SD)	5.02 (3.58)	6.38 (3.07)
SE	0.41	0.59
Median	5.00	7.00
Min, Max	0.0, 10.0	1.0, 10.0
Month 9		
Actual Value		
n	73	25
Mean (SD)	5.01 (3.57)	6.44 (3.04)
SE	0.42	0.61
Median	5.00	7.50
Min, Max	0.0, 10.0	1.0, 10.0
Change from baseline		
n	73	25
Mean (SD)	0.10 (0.92)	0.17 (0.77)
SE	0.11	0.15
Median	0.00	0.00
Min, Max	-2.5, 3.0	-1.2, 2.0

mNIS+7 score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurologic impairment (range = 0 to 304). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 2.8
Modified Neuropathy Impairment Score +7 (mNIS+7) Components: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Component: Nerve Conduction Study (NCS)

Weight (kg): ≥65

Subgroup Visit	Vutrisiran (HELIOS-A) (N=76)	Patisiran (HELIOS-A) (N=27)
Month 18		
Actual Value		
n	73	23
Mean (SD)	4.99 (3.73)	6.61 (3.04)
SE	0.44	0.63
Median	5.50	7.50
Min, Max	0.0, 10.0	1.0, 10.0
Change from baseline		
n	73	23
Mean (SD)	-0.02 (1.11)	0.41 (0.94)
SE	0.13	0.20
Median	0.00	0.00
Min, Max	-4.0, 3.5	-1.2, 2.5

mNIS+7 score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurologic impairment (range = 0 to 304). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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mNIS+7 – Domäne Lageabhängiger Blutdruck

Alnylam Pharmaceuticals Inc.
ALN-TTRSC02-002

Table 2.6
Modified Neuropathy Impairment Score +7 (mNIS+7) Component Scores: Change from Baseline to Month 18, MMRM Model
Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A) Subgroup Analysis
mITT Population

Postural Blood Pressure (PBP)

Subgroup Visit	LS Mean (95% CI) Vutrisiran (HELIOS-A) (N=122)	LS Mean (95% CI) Patisiran (HELIOS-A) (N=42)	LS Mean Difference (Vutrisiran-Patisiran) (95% CI), p-value	Standardized Effect Size (95% CI)
Age (years)				
<65	75	30		
Month 9	0.03 (-0.09, 0.15)	-0.08 (-0.27, 0.12)	0.10 (-0.12, 0.33), 0.3660	0.19 (-0.23, 0.61)
Month 18	0.07 (-0.05, 0.19)	0.03 (-0.17, 0.23)	0.04 (-0.20, 0.27), 0.7580	0.06 (-0.36, 0.49)
≥65	44	10		
Month 9	-0.04 (-0.19, 0.12)	0.02 (-0.29, 0.33)	-0.05 (-0.40, 0.29), 0.7635	-0.09 (-0.77, 0.59)
Month 18	0.01 (-0.15, 0.16)	0.13 (-0.19, 0.44)	-0.12 (-0.47, 0.23), 0.5007	-0.21 (-0.92, 0.50)
p-value of Treatment*Age	0.4234			

mNIS+7 score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurologic impairment (range = 0 to 304). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.
LS estimates and p-value derived from mixed-effects model for repeated measures (MMRM), controlling for categorical factors (treatment, visit), the subgroup variable, continuous covariate (baseline value), and interaction (treatment by visit, treatment by subgroup).
Standardized effect size (d) = LS mean difference/estimated pooled standard deviation with the small sample bias correction.

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Table 2.6
Modified Neuropathy Impairment Score +7 (mNIS+7) Component Scores: Change from Baseline to Month 18, MMRM Model
Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A) Subgroup Analysis
mITT Population

Postural Blood Pressure (PBP)

Subgroup Visit	LS Mean (95% CI) Vutrisiran (HELIOS-A) (N=122)	LS Mean (95% CI) Patisiran (HELIOS-A) (N=42)	LS Mean Difference (Vutrisiran-Patisiran) (95% CI), p-value	Standardized Effect Size (95% CI)
Sex				
Male	77	25		
Month 9	0.00 (-0.11, 0.12)	-0.01 (-0.22, 0.20)	0.01 (-0.22, 0.25), 0.9042	0.03 (-0.42, 0.48)
Month 18	0.05 (-0.08, 0.17)	0.10 (-0.12, 0.31)	-0.05 (-0.30, 0.19), 0.6721	-0.10 (-0.57, 0.36)
Female	42	15		
Month 9	0.00 (-0.15, 0.16)	-0.13 (-0.38, 0.13)	0.13 (-0.17, 0.43), 0.3913	0.22 (-0.37, 0.80)
Month 18	0.05 (-0.11, 0.20)	-0.02 (-0.28, 0.24)	0.06 (-0.24, 0.37), 0.6851	0.10 (-0.49, 0.68)
p-value of Treatment*Sex	0.5180			

mNIS+7 score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurologic impairment (range = 0 to 304). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.
LS estimates and p-value derived from mixed-effects model for repeated measures (MMRM), controlling for categorical factors (treatment, visit), the subgroup variable, continuous covariate (baseline value), and interaction (treatment by visit, treatment by subgroup).
Standardized effect size (d) = LS mean difference/estimated pooled standard deviation with the small sample bias correction.

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Table 2.6
Modified Neuropathy Impairment Score +7 (mNIS+7) Component Scores: Change from Baseline to Month 18, MMRM Model
Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A) Subgroup Analysis
mITT Population

Postural Blood Pressure (PBP)

Subgroup Visit	LS Mean (95% CI) Vutrisiran (HELIOS-A) (N=122)	LS Mean (95% CI) Patisiran (HELIOS-A) (N=42)	LS Mean Difference (Vutrisiran-Patisiran) (95% CI), p-value	Standardized Effect Size (95% CI)
Race				
White	84	28		
Month 9	0.02 (-0.09, 0.14)	-0.05 (-0.25, 0.15)	0.07 (-0.16, 0.30), 0.5459	0.13 (-0.29, 0.56)
Month 18	0.06 (-0.05, 0.18)	0.06 (-0.15, 0.26)	0.00 (-0.23, 0.24), 0.9732	0.01 (-0.42, 0.44)
All Other Races	35	12		
Month 9	-0.04 (-0.21, 0.13)	-0.07 (-0.35, 0.22)	0.03 (-0.30, 0.36), 0.8649	0.05 (-0.60, 0.70)
Month 18	0.00 (-0.17, 0.17)	0.04 (-0.25, 0.33)	-0.04 (-0.37, 0.30), 0.8243	-0.06 (-0.73, 0.61)
p-value of Treatment*Race	0.8258			

mNIS+7 score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurologic impairment (range = 0 to 304). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.
LS estimates and p-value derived from mixed-effects model for repeated measures (MMRM), controlling for categorical factors (treatment, visit), the subgroup variable, continuous covariate (baseline value), and interaction (treatment by visit, treatment by subgroup).
Standardized effect size (d) = LS mean difference/estimated pooled standard deviation with the small sample bias correction.

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Table 2.6
Modified Neuropathy Impairment Score +7 (mNIS+7) Component Scores: Change from Baseline to Month 18, MMRM Model
Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A) Subgroup Analysis
mITT Population

Postural Blood Pressure (PBP)

Subgroup Visit	LS Mean (95% CI) Vutrisiran (HELIOS-A) (N=122)	LS Mean (95% CI) Patisiran (HELIOS-A) (N=42)	LS Mean Difference (Vutrisiran-Patisiran) (95% CI), p-value	Standardized Effect Size (95% CI)
Region				
North America	27	8		
Month 9	-0.04 (-0.23, 0.15)	-0.29 (-0.63, 0.04)	0.25 (-0.13, 0.64), 0.1931	0.82 (0.02, 1.62)
Month 18	0.00 (-0.18, 0.19)	-0.19 (-0.53, 0.15)	0.19 (-0.20, 0.58), 0.3294	0.40 (-0.42, 1.22)
Western Europe	40	18		
Month 9	-0.11 (-0.27, 0.04)	0.11 (-0.12, 0.35)	-0.23 (-0.51, 0.05), 0.1099	-0.41 (-0.97, 0.14)
Month 18	-0.07 (-0.23, 0.08)	0.22 (-0.02, 0.45)	-0.29 (-0.57, -0.01), 0.0453	-0.63 (-1.19, -0.07)
Rest of World	52	14		
Month 9	0.11 (-0.02, 0.25)	-0.13 (-0.39, 0.13)	0.24 (-0.05, 0.53), 0.1081	0.38 (-0.21, 0.97)
Month 18	0.16 (0.02, 0.30)	-0.02 (-0.29, 0.24)	0.18 (-0.12, 0.48), 0.2394	0.27 (-0.34, 0.87)
p-value of Treatment*Region	0.0246			

mNIS+7 score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurologic impairment (range = 0 to 304). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.
LS estimates and p-value derived from mixed-effects model for repeated measures (MMRM), controlling for categorical factors (treatment, visit), the subgroup variable, continuous covariate (baseline value), and interaction (treatment by visit, treatment by subgroup).
Standardized effect size (d) = LS mean difference/estimated pooled standard deviation with the small sample bias correction.

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ALN-TTRSC02-002

Table 2.6
Modified Neuropathy Impairment Score +7 (mNIS+7) Component Scores: Change from Baseline to Month 18, MMRM Model
Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A) Subgroup Analysis
mITT Population

Postural Blood Pressure (PBP)

Subgroup Visit	LS Mean (95% CI) Vutrisiran (HELIOS-A) (N=122)	LS Mean (95% CI) Patisiran (HELIOS-A) (N=42)	LS Mean Difference (Vutrisiran-Patisiran) (95% CI), p-value	Standardized Effect Size (95% CI)
Baseline NIS				
<50	77	27		
Month 9	-0.02 (-0.14, 0.09)	-0.08 (-0.28, 0.12)	0.05 (-0.18, 0.28), 0.6571	0.11 (-0.32, 0.55)
Month 18	0.02 (-0.10, 0.14)	0.03 (-0.17, 0.24)	-0.01 (-0.26, 0.23), 0.9025	-0.03 (-0.47, 0.41)
≥50	42	13		
Month 9	0.06 (-0.10, 0.21)	-0.01 (-0.28, 0.27)	0.06 (-0.25, 0.38), 0.6972	0.09 (-0.53, 0.71)
Month 18	0.10 (-0.06, 0.25)	0.10 (-0.18, 0.38)	-0.01 (-0.33, 0.32), 0.9742	-0.01 (-0.64, 0.63)
p-value of Treatment*Baseline NIS	0.9579			

mNIS+7 score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurologic impairment (range = 0 to 304). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.
LS estimates and p-value derived from mixed-effects model for repeated measures (MMRM), controlling for categorical factors (treatment, visit), the subgroup variable, continuous covariate (baseline value), and interaction (treatment by visit, treatment by subgroup).
Standardized effect size (d) = LS mean difference/estimated pooled standard deviation with the small sample bias correction.

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Table 2.6
Modified Neuropathy Impairment Score +7 (mNIS+7) Component Scores: Change from Baseline to Month 18, MMRM Model
Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A) Subgroup Analysis
mITT Population

Postural Blood Pressure (PBP)

Subgroup Visit	LS Mean (95% CI) Vutrisiran (HELIOS-A) (N=122)	LS Mean (95% CI) Patisiran (HELIOS-A) (N=42)	LS Mean Difference (Vutrisiran-Patisiran) (95% CI), p-value	Standardized Effect Size (95% CI)
Previous Tetramer Stabilizer Use				
Yes	74	32		
Month 9	0.06 (-0.06, 0.18)	-0.04 (-0.22, 0.15)	0.10 (-0.13, 0.32), 0.3938	0.16 (-0.25, 0.57)
Month 18	0.10 (-0.02, 0.23)	0.07 (-0.12, 0.26)	0.03 (-0.20, 0.26), 0.7884	0.06 (-0.36, 0.48)
No	45	8		
Month 9	-0.09 (-0.24, 0.06)	-0.12 (-0.46, 0.22)	0.03 (-0.34, 0.40), 0.8651	0.08 (-0.67, 0.82)
Month 18	-0.05 (-0.20, 0.10)	-0.01 (-0.36, 0.33)	-0.03 (-0.41, 0.35), 0.8666	-0.05 (-0.84, 0.73)
p-value of Treatment*Previous Tetramer Stabilizer Use	0.7586			

mNIS+7 score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurologic impairment (range = 0 to 304). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.
LS estimates and p-value derived from mixed-effects model for repeated measures (MMRM), controlling for categorical factors (treatment, visit), the subgroup variable, continuous covariate (baseline value), and interaction (treatment by visit, treatment by subgroup).
Standardized effect size (d) = LS mean difference/estimated pooled standard deviation with the small sample bias correction.

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Table 2.6
Modified Neuropathy Impairment Score +7 (mNIS+7) Component Scores: Change from Baseline to Month 18, MMRM Model
Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A) Subgroup Analysis
mITT Population

Postural Blood Pressure (PBP)

Subgroup Visit	LS Mean (95% CI) Vutrisiran (HELIOS-A) (N=122)	LS Mean (95% CI) Patisiran (HELIOS-A) (N=42)	LS Mean Difference (Vutrisiran-Patisiran) (95% CI), p-value	Standardized Effect Size (95% CI)
Genotype				
V30M	53	20		
Month 9	0.00 (-0.14, 0.14)	0.05 (-0.18, 0.27)	-0.04 (-0.31, 0.22), 0.7527	-0.08 (-0.59, 0.43)
Month 18	0.05 (-0.10, 0.19)	0.15 (-0.08, 0.38)	-0.11 (-0.38, 0.17), 0.4418	-0.19 (-0.70, 0.33)
non-V30M	66	20		
Month 9	0.00 (-0.12, 0.13)	-0.15 (-0.38, 0.07)	0.16 (-0.10, 0.42), 0.2303	0.27 (-0.22, 0.77)
Month 18	0.05 (-0.08, 0.18)	-0.05 (-0.28, 0.19)	0.09 (-0.18, 0.36), 0.4919	0.16 (-0.35, 0.68)
p-value of Treatment*Genotype	0.2499			

mNIS+7 score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurologic impairment (range = 0 to 304). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.
LS estimates and p-value derived from mixed-effects model for repeated measures (MMRM), controlling for categorical factors (treatment, visit), the subgroup variable, continuous covariate (baseline value), and interaction (treatment by visit, treatment by subgroup).
Standardized effect size (d) = LS mean difference/estimated pooled standard deviation with the small sample bias correction.

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Table 2.6
Modified Neuropathy Impairment Score +7 (mNIS+7) Component Scores: Change from Baseline to Month 18, MMRM Model
Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A) Subgroup Analysis
mITT Population

Postural Blood Pressure (PBP)

Subgroup Visit	LS Mean (95% CI) Vutrisiran (HELIOS-A) (N=122)	LS Mean (95% CI) Patisiran (HELIOS-A) (N=42)	LS Mean Difference (Vutrisiran-Patisiran) (95% CI), p-value	Standardized Effect Size (95% CI)
FAP Stage				
I	83	30		
Month 9	-0.05 (-0.16, 0.06)	-0.07 (-0.26, 0.12)	0.02 (-0.20, 0.24), 0.8747	0.04 (-0.38, 0.45)
Month 18	-0.01 (-0.13, 0.11)	0.04 (-0.16, 0.24)	-0.05 (-0.28, 0.18), 0.6700	-0.10 (-0.51, 0.32)
II&III	36	10		
Month 9	0.13 (-0.03, 0.29)	-0.00 (-0.31, 0.30)	0.14 (-0.21, 0.48), 0.4409	0.20 (-0.49, 0.89)
Month 18	0.17 (0.01, 0.34)	0.10 (-0.22, 0.43)	0.07 (-0.29, 0.43), 0.7105	0.09 (-0.66, 0.85)
p-value of Treatment*FAP Stage	0.5503			

mNIS+7 score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurologic impairment (range = 0 to 304). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.
LS estimates and p-value derived from mixed-effects model for repeated measures (MMRM), controlling for categorical factors (treatment, visit), the subgroup variable, continuous covariate (baseline value), and interaction (treatment by visit, treatment by subgroup).
Standardized effect size (d) = LS mean difference/estimated pooled standard deviation with the small sample bias correction.

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Table 2.6
Modified Neuropathy Impairment Score +7 (mNIS+7) Component Scores: Change from Baseline to Month 18, MMRM Model
Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A) Subgroup Analysis
mITT Population

Postural Blood Pressure (PBP)

Subgroup Visit	LS Mean (95% CI) Vutrisiran (HELIOS-A) (N=122)	LS Mean (95% CI) Patisiran (HELIOS-A) (N=42)	LS Mean Difference (Vutrisiran-Patisiran) (95% CI), p-value	Standardized Effect Size (95% CI)
Cardiac Subpopulation				
Yes	38	14		
Month 9	0.18 (0.02, 0.34)	0.04 (-0.22, 0.30)	0.14 (-0.16, 0.44), 0.3619	0.20 (-0.40, 0.81)
Month 18	0.22 (0.06, 0.39)	0.15 (-0.12, 0.42)	0.07 (-0.24, 0.39), 0.6490	0.11 (-0.51, 0.73)
No	81	26		
Month 9	-0.08 (-0.20, 0.03)	-0.10 (-0.30, 0.10)	0.02 (-0.21, 0.25), 0.8801	0.04 (-0.40, 0.48)
Month 18	-0.04 (-0.16, 0.08)	0.01 (-0.20, 0.22)	-0.05 (-0.29, 0.19), 0.6880	-0.09 (-0.54, 0.35)
p-value of Treatment*Cardiac Subpopulation	0.5011			

mNIS+7 score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurologic impairment (range = 0 to 304). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.
LS estimates and p-value derived from mixed-effects model for repeated measures (MMRM), controlling for categorical factors (treatment, visit), the subgroup variable, continuous covariate (baseline value), and interaction (treatment by visit, treatment by subgroup).
Standardized effect size (d) = LS mean difference/estimated pooled standard deviation with the small sample bias correction.

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Table 2.6
Modified Neuropathy Impairment Score +7 (mNIS+7) Component Scores: Change from Baseline to Month 18, MMRM Model
Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A) Subgroup Analysis
mITT Population

Postural Blood Pressure (PBP)

Subgroup Visit	LS Mean (95% CI) Vutrisiran (HELIOS-A) (N=122)	LS Mean (95% CI) Patisiran (HELIOS-A) (N=42)	LS Mean Difference (Vutrisiran-Patisiran) (95% CI), p-value	Standardized Effect Size (95% CI)
Weight (kg)				
<65	44	15		
Month 9	0.05 (-0.10, 0.20)	0.10 (-0.16, 0.36)	-0.05 (-0.34, 0.25), 0.7565	-0.07 (-0.65, 0.51)
Month 18	0.09 (-0.06, 0.25)	0.20 (-0.06, 0.46)	-0.11 (-0.41, 0.19), 0.4676	-0.16 (-0.75, 0.42)
≥65	75	25		
Month 9	-0.03 (-0.15, 0.10)	-0.14 (-0.35, 0.06)	0.12 (-0.12, 0.36), 0.3381	0.25 (-0.20, 0.70)
Month 18	0.02 (-0.11, 0.14)	-0.04 (-0.25, 0.18)	0.05 (-0.19, 0.30), 0.6726	0.11 (-0.36, 0.57)
p-value of Treatment*Weight	0.3585			

mNIS+7 score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurologic impairment (range = 0 to 304). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.
LS estimates and p-value derived from mixed-effects model for repeated measures (MMRM), controlling for categorical factors (treatment, visit), the subgroup variable, continuous covariate (baseline value), and interaction (treatment by visit, treatment by subgroup).
Standardized effect size (d) = LS mean difference/estimated pooled standard deviation with the small sample bias correction.

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Table 2.8
Modified Neuropathy Impairment Score +7 (mNIS+7) Components: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Component: Postural Blood Pressure (PBP)

Age (years): <65

Subgroup Visit	Vutrisiran (HELIOS-A) (N=76)	Patisiran (HELIOS-A) (N=31)
Baseline		
n	76	31
Mean (SD)	0.41 (0.69)	0.47 (0.77)
SE	0.08	0.14
Median	0.00	0.00
Min, Max	0.0, 2.0	0.0, 2.0
Month 9		
Actual Value		
n	74	30
Mean (SD)	0.40 (0.67)	0.35 (0.67)
SE	0.08	0.12
Median	0.00	0.00
Min, Max	0.0, 2.0	0.0, 2.0
Change from baseline		
n	74	30
Mean (SD)	0.01 (0.60)	-0.13 (0.68)
SE	0.07	0.12
Median	0.00	0.00
Min, Max	-2.0, 2.0	-2.0, 2.0

mNIS+7 score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurologic impairment (range = 0 to 304). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 2.8
Modified Neuropathy Impairment Score +7 (mNIS+7) Components: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Component: Postural Blood Pressure (PBP)

Age (years): <65

Subgroup Visit	Vutrisiran (HELIOS-A) (N=76)	Patisiran (HELIOS-A) (N=31)
Month 18		
Actual Value		
n	74	29
Mean (SD)	0.47 (0.70)	0.50 (0.69)
SE	0.08	0.13
Median	0.00	0.00
Min, Max	0.0, 2.0	0.0, 2.0
Change from baseline		
n	74	29
Mean (SD)	0.07 (0.68)	0.00 (0.55)
SE	0.08	0.10
Median	0.00	0.00
Min, Max	-2.0, 1.5	-1.5, 1.5

mNIS+7 score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurologic impairment (range = 0 to 304). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 2.8
Modified Neuropathy Impairment Score +7 (mNIS+7) Components: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Component: Postural Blood Pressure (PBP)

Age (years): ≥65

Subgroup Visit	Vutrisiran (HELIOS-A) (N=46)	Patisiran (HELIOS-A) (N=11)
Baseline		
n	46	11
Mean (SD)	0.26 (0.42)	0.36 (0.45)
SE	0.06	0.14
Median	0.00	0.00
Min, Max	0.0, 1.5	0.0, 1.0
Month 9		
Actual Value		
n	43	10
Mean (SD)	0.31 (0.68)	0.45 (0.72)
SE	0.10	0.23
Median	0.00	0.00
Min, Max	0.0, 2.0	0.0, 2.0
Change from baseline		
n	43	10
Mean (SD)	0.03 (0.55)	0.05 (0.55)
SE	0.08	0.17
Median	0.00	0.00
Min, Max	-1.0, 1.5	-0.5, 1.0

mNIS+7 score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurologic impairment (range = 0 to 304). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 2.8
Modified Neuropathy Impairment Score +7 (mNIS+7) Components: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Component: Postural Blood Pressure (PBP)

Age (years): ≥65

Subgroup Visit	Vutrisiran (HELIOS-A) (N=46)	Patisiran (HELIOS-A) (N=11)
Month 18		
Actual Value		
n	41	9
Mean (SD)	0.29 (0.59)	0.50 (0.79)
SE	0.09	0.26
Median	0.00	0.00
Min, Max	0.0, 2.0	0.0, 2.0
Change from baseline		
n	41	9
Mean (SD)	0.02 (0.56)	0.06 (0.68)
SE	0.09	0.23
Median	0.00	0.00
Min, Max	-1.0, 1.5	-1.0, 1.5

mNIS+7 score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurologic impairment (range = 0 to 304). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 2.8
Modified Neuropathy Impairment Score +7 (mNIS+7) Components: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Component: Postural Blood Pressure (PBP)

Sex: Male

Subgroup Visit	Vutrisiran (HELIOS-A) (N=79)	Patisiran (HELIOS-A) (N=27)
Baseline		
n	79	27
Mean (SD)	0.37 (0.63)	0.41 (0.65)
SE	0.07	0.13
Median	0.00	0.00
Min, Max	0.0, 2.0	0.0, 2.0
Month 9		
Actual Value		
n	76	25
Mean (SD)	0.39 (0.70)	0.44 (0.74)
SE	0.08	0.15
Median	0.00	0.00
Min, Max	0.0, 2.0	0.0, 2.0
Change from baseline		
n	76	25
Mean (SD)	0.01 (0.50)	0.00 (0.65)
SE	0.06	0.13
Median	0.00	0.00
Min, Max	-1.5, 2.0	-1.0, 2.0

mNIS+7 score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurologic impairment (range = 0 to 304). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 2.8
Modified Neuropathy Impairment Score +7 (mNIS+7) Components: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Component: Postural Blood Pressure (PBP)

Sex: Male

Subgroup Visit	Vutrisiran (HELIOS-A) (N=79)	Patisiran (HELIOS-A) (N=27)
Month 18		
Actual Value		
n	74	23
Mean (SD)	0.42 (0.69)	0.50 (0.69)
SE	0.08	0.14
Median	0.00	0.00
Min, Max	0.0, 2.0	0.0, 2.0
Change from baseline		
n	74	23
Mean (SD)	0.03 (0.54)	0.02 (0.55)
SE	0.06	0.12
Median	0.00	0.00
Min, Max	-2.0, 1.5	-1.0, 1.5

mNIS+7 score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurologic impairment (range = 0 to 304). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 2.8
Modified Neuropathy Impairment Score +7 (mNIS+7) Components: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Component: Postural Blood Pressure (PBP)

Sex: Female

Subgroup Visit	Vutrisiran (HELIOS-A) (N=43)	Patisiran (HELIOS-A) (N=15)
Baseline		
n	43	15
Mean (SD)	0.33 (0.57)	0.50 (0.80)
SE	0.09	0.21
Median	0.00	0.00
Min, Max	0.0, 2.0	0.0, 2.0
Month 9		
Actual Value		
n	41	15
Mean (SD)	0.32 (0.62)	0.27 (0.56)
SE	0.10	0.15
Median	0.00	0.00
Min, Max	0.0, 2.0	0.0, 1.5
Change from baseline		
n	41	15
Mean (SD)	0.02 (0.72)	-0.23 (0.65)
SE	0.11	0.17
Median	0.00	0.00
Min, Max	-2.0, 2.0	-2.0, 1.0

mNIS+7 score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurologic impairment (range = 0 to 304). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 2.8
Modified Neuropathy Impairment Score +7 (mNIS+7) Components: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Component: Postural Blood Pressure (PBP)

Sex: Female

Subgroup Visit	Vutrisiran (HELIOS-A) (N=43)	Patisiran (HELIOS-A) (N=15)
Month 18		
Actual Value		
n	41	15
Mean (SD)	0.39 (0.62)	0.50 (0.76)
SE	0.10	0.20
Median	0.00	0.00
Min, Max	0.0, 2.0	0.0, 2.0
Change from baseline		
n	41	15
Mean (SD)	0.10 (0.78)	0.00 (0.63)
SE	0.12	0.16
Median	0.00	0.00
Min, Max	-2.0, 1.5	-1.5, 1.5

mNIS+7 score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurologic impairment (range = 0 to 304). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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ALN-TTRSC02-002

Table 2.8
Modified Neuropathy Impairment Score +7 (mNIS+7) Components: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Component: Postural Blood Pressure (PBP)

Race: White

Subgroup Visit	Vutrisiran (HELIOS-A) (N=86)	Patisiran (HELIOS-A) (N=29)
Baseline		
n	86	29
Mean (SD)	0.28 (0.55)	0.48 (0.71)
SE	0.06	0.13
Median	0.00	0.00
Min, Max	0.0, 2.0	0.0, 2.0
Month 9		
Actual Value		
n	83	28
Mean (SD)	0.34 (0.66)	0.39 (0.71)
SE	0.07	0.13
Median	0.00	0.00
Min, Max	0.0, 2.0	0.0, 2.0
Change from baseline		
n	83	28
Mean (SD)	0.05 (0.51)	-0.11 (0.72)
SE	0.06	0.14
Median	0.00	0.00
Min, Max	-1.5, 2.0	-2.0, 2.0

mNIS+7 score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurologic impairment (range = 0 to 304). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

Alnylam Pharmaceuticals Inc.
ALN-TTRSC02-002

Table 2.8
Modified Neuropathy Impairment Score +7 (mNIS+7) Components: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Component: Postural Blood Pressure (PBP)

Race: White

Subgroup Visit	Vutrisiran (HELIOS-A) (N=86)	Patisiran (HELIOS-A) (N=29)
Month 18		
Actual Value		
n	82	27
Mean (SD)	0.39 (0.65)	0.54 (0.75)
SE	0.07	0.14
Median	0.00	0.00
Min, Max	0.0, 2.0	0.0, 2.0
Change from baseline		
n	82	27
Mean (SD)	0.10 (0.55)	0.02 (0.60)
SE	0.06	0.11
Median	0.00	0.00
Min, Max	-2.0, 1.5	-1.5, 1.5

mNIS+7 score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurologic impairment (range = 0 to 304). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Alnylam Pharmaceuticals Inc.
ALN-TTRSC02-002

Table 2.8
Modified Neuropathy Impairment Score +7 (mNIS+7) Components: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Component: Postural Blood Pressure (PBP)

Race: All Other Races

Subgroup Visit	Vutrisiran (HELIOS-A) (N=36)	Patisiran (HELIOS-A) (N=13)
Baseline		
n	36	13
Mean (SD)	0.54 (0.69)	0.35 (0.69)
SE	0.12	0.19
Median	0.25	0.00
Min, Max	0.0, 2.0	0.0, 2.0
Month 9		
Actual Value		
n	34	12
Mean (SD)	0.43 (0.70)	0.33 (0.62)
SE	0.12	0.18
Median	0.00	0.00
Min, Max	0.0, 2.0	0.0, 2.0
Change from baseline		
n	34	12
Mean (SD)	-0.07 (0.73)	-0.04 (0.45)
SE	0.13	0.13
Median	0.00	0.00
Min, Max	-2.0, 2.0	-1.0, 1.0

mNIS+7 score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurologic impairment (range = 0 to 304). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Alnylam Pharmaceuticals Inc.
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Table 2.8
Modified Neuropathy Impairment Score +7 (mNIS+7) Components: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Component: Postural Blood Pressure (PBP)

Race: All Other Races

Subgroup Visit	Vutrisiran (HELIOS-A) (N=36)	Patisiran (HELIOS-A) (N=13)
Month 18		
Actual Value		
n	33	11
Mean (SD)	0.45 (0.70)	0.41 (0.63)
SE	0.12	0.19
Median	0.00	0.00
Min, Max	0.0, 2.0	0.0, 2.0
Change from baseline		
n	33	11
Mean (SD)	-0.05 (0.81)	0.00 (0.55)
SE	0.14	0.17
Median	0.00	0.00
Min, Max	-2.0, 1.5	-1.0, 0.5

mNIS+7 score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurologic impairment (range = 0 to 304). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

Alnylam Pharmaceuticals Inc.
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Table 2.8
Modified Neuropathy Impairment Score +7 (mNIS+7) Components: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Component: Postural Blood Pressure (PBP)

Region: North America

Subgroup Visit	Vutrisiran (HELIOS-A) (N=27)	Patisiran (HELIOS-A) (N=8)
Baseline		
n	27	8
Mean (SD)	0.19 (0.44)	0.25 (0.71)
SE	0.09	0.25
Median	0.00	0.00
Min, Max	0.0, 2.0	0.0, 2.0
Month 9		
Actual Value		
n	25	8
Mean (SD)	0.22 (0.46)	0.00 (0.00)
SE	0.09	0.00
Median	0.00	0.00
Min, Max	0.0, 2.0	0.0, 0.0
Change from baseline		
n	25	8
Mean (SD)	0.04 (0.25)	-0.25 (0.71)
SE	0.05	0.25
Median	0.00	0.00
Min, Max	-0.5, 0.5	-2.0, 0.0

mNIS+7 score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurologic impairment (range = 0 to 304). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Alnylam Pharmaceuticals Inc.
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Table 2.8
Modified Neuropathy Impairment Score +7 (mNIS+7) Components: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Component: Postural Blood Pressure (PBP)

Region: North America

Subgroup Visit	Vutrisiran (HELIOS-A) (N=27)	Patisiran (HELIOS-A) (N=8)
Month 18		
Actual Value		
n	25	7
Mean (SD)	0.30 (0.63)	0.14 (0.24)
SE	0.13	0.09
Median	0.00	0.00
Min, Max	0.0, 2.0	0.0, 0.5
Change from baseline		
n	25	7
Mean (SD)	0.10 (0.50)	-0.14 (0.63)
SE	0.10	0.24
Median	0.00	0.00
Min, Max	-1.0, 1.5	-1.5, 0.5

mNIS+7 score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurologic impairment (range = 0 to 304). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Alnylam Pharmaceuticals Inc.
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Table 2.8
Modified Neuropathy Impairment Score +7 (mNIS+7) Components: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Component: Postural Blood Pressure (PBP)

Region: Western Europe

Subgroup Visit	Vutrisiran (HELIOS-A) (N=42)	Patisiran (HELIOS-A) (N=20)
Baseline		
n	42	20
Mean (SD)	0.26 (0.51)	0.43 (0.65)
SE	0.08	0.15
Median	0.00	0.00
Min, Max	0.0, 2.0	0.0, 2.0
Month 9		
Actual Value		
n	40	18
Mean (SD)	0.24 (0.59)	0.56 (0.82)
SE	0.09	0.19
Median	0.00	0.00
Min, Max	0.0, 2.0	0.0, 2.0
Change from baseline		
n	40	18
Mean (SD)	-0.04 (0.51)	0.08 (0.69)
SE	0.08	0.16
Median	0.00	0.00
Min, Max	-2.0, 1.0	-1.0, 2.0

mNIS+7 score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurologic impairment (range = 0 to 304). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 2.8
Modified Neuropathy Impairment Score +7 (mNIS+7) Components: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Component: Postural Blood Pressure (PBP)

Region: Western Europe

Subgroup Visit	Vutrisiran (HELIOS-A) (N=42)	Patisiran (HELIOS-A) (N=20)
Month 18		
Actual Value		
n	40	18
Mean (SD)	0.21 (0.47)	0.64 (0.82)
SE	0.07	0.19
Median	0.00	0.00
Min, Max	0.0, 2.0	0.0, 2.0
Change from baseline		
n	40	18
Mean (SD)	-0.06 (0.46)	0.17 (0.54)
SE	0.07	0.13
Median	0.00	0.00
Min, Max	-2.0, 1.0	-0.5, 1.5

mNIS+7 score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurologic impairment (range = 0 to 304). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Alnylam Pharmaceuticals Inc.
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Table 2.8
Modified Neuropathy Impairment Score +7 (mNIS+7) Components: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Component: Postural Blood Pressure (PBP)

Region: Rest of World

Subgroup Visit	Vutrisiran (HELIOS-A) (N=53)	Patisiran (HELIOS-A) (N=14)
Baseline		
n	53	14
Mean (SD)	0.52 (0.71)	0.57 (0.78)
SE	0.10	0.21
Median	0.00	0.00
Min, Max	0.0, 2.0	0.0, 2.0
Month 9		
Actual Value		
n	52	14
Mean (SD)	0.54 (0.78)	0.36 (0.60)
SE	0.11	0.16
Median	0.00	0.00
Min, Max	0.0, 2.0	0.0, 2.0
Change from baseline		
n	52	14
Mean (SD)	0.05 (0.73)	-0.21 (0.54)
SE	0.10	0.15
Median	0.00	0.00
Min, Max	-1.5, 2.0	-1.0, 1.0

mNIS+7 score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurologic impairment (range = 0 to 304). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Alnylam Pharmaceuticals Inc.
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Table 2.8
Modified Neuropathy Impairment Score +7 (mNIS+7) Components: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Component: Postural Blood Pressure (PBP)

Region: Rest of World

Subgroup Visit	Vutrisiran (HELIOS-A) (N=53)	Patisiran (HELIOS-A) (N=14)
Month 18		
Actual Value		
n	50	13
Mean (SD)	0.62 (0.76)	0.50 (0.68)
SE	0.11	0.19
Median	0.50	0.00
Min, Max	0.0, 2.0	0.0, 2.0
Change from baseline		
n	50	13
Mean (SD)	0.13 (0.79)	-0.12 (0.58)
SE	0.11	0.16
Median	0.00	0.00
Min, Max	-2.0, 1.5	-1.0, 0.5

mNIS+7 score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurologic impairment (range = 0 to 304). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Alnylam Pharmaceuticals Inc.
ALN-TTRSC02-002

Table 2.8
Modified Neuropathy Impairment Score +7 (mNIS+7) Components: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Component: Postural Blood Pressure (PBP)

Baseline NIS: <50

Subgroup Visit	Vutrisiran (HELIOS-A) (N=78)	Patisiran (HELIOS-A) (N=27)
Baseline		
n	78	27
Mean (SD)	0.32 (0.58)	0.41 (0.76)
SE	0.07	0.15
Median	0.00	0.00
Min, Max	0.0, 2.0	0.0, 2.0
Month 9		
Actual Value		
n	77	27
Mean (SD)	0.28 (0.59)	0.33 (0.62)
SE	0.07	0.12
Median	0.00	0.00
Min, Max	0.0, 2.0	0.0, 2.0
Change from baseline		
n	77	27
Mean (SD)	-0.02 (0.44)	-0.07 (0.68)
SE	0.05	0.13
Median	0.00	0.00
Min, Max	-1.0, 2.0	-2.0, 2.0

mNIS+7 score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurologic impairment (range = 0 to 304). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Alnylam Pharmaceuticals Inc.
ALN-TTRSC02-002

Table 2.8
Modified Neuropathy Impairment Score +7 (mNIS+7) Components: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Component: Postural Blood Pressure (PBP)

Baseline NIS: <50

Subgroup Visit	Vutrisiran (HELIOS-A) (N=78)	Patisiran (HELIOS-A) (N=27)
Month 18		
Actual Value		
n	75	26
Mean (SD)	0.39 (0.66)	0.42 (0.69)
SE	0.08	0.13
Median	0.00	0.00
Min, Max	0.0, 2.0	0.0, 2.0
Change from baseline		
n	75	26
Mean (SD)	0.08 (0.52)	0.00 (0.53)
SE	0.06	0.10
Median	0.00	0.00
Min, Max	-1.0, 1.5	-1.5, 1.5

mNIS+7 score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurologic impairment (range = 0 to 304). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Alnylam Pharmaceuticals Inc.
ALN-TTRSC02-002

Table 2.8
Modified Neuropathy Impairment Score +7 (mNIS+7) Components: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Component: Postural Blood Pressure (PBP)

Baseline NIS: ≥50

Subgroup Visit	Vutrisiran (HELIOS-A) (N=44)	Patisiran (HELIOS-A) (N=15)
Baseline		
n	44	15
Mean (SD)	0.42 (0.66)	0.50 (0.60)
SE	0.10	0.15
Median	0.00	0.50
Min, Max	0.0, 2.0	0.0, 2.0
Month 9		
Actual Value		
n	40	13
Mean (SD)	0.54 (0.79)	0.46 (0.80)
SE	0.12	0.22
Median	0.00	0.00
Min, Max	0.0, 2.0	0.0, 2.0
Change from baseline		
n	40	13
Mean (SD)	0.09 (0.78)	-0.12 (0.62)
SE	0.12	0.17
Median	0.00	0.00
Min, Max	-2.0, 2.0	-1.0, 1.0

mNIS+7 score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurologic impairment (range = 0 to 304). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 2.8
Modified Neuropathy Impairment Score +7 (mNIS+7) Components: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Component: Postural Blood Pressure (PBP)

Baseline NIS: ≥50

Subgroup Visit	Vutrisiran (HELIOS-A) (N=44)	Patisiran (HELIOS-A) (N=15)
Month 18		
Actual Value		
n	40	12
Mean (SD)	0.45 (0.68)	0.67 (0.75)
SE	0.11	0.22
Median	0.00	0.50
Min, Max	0.0, 2.0	0.0, 2.0
Change from baseline		
n	40	12
Mean (SD)	0.01 (0.81)	0.04 (0.69)
SE	0.13	0.20
Median	0.00	0.00
Min, Max	-2.0, 1.5	-1.0, 1.5

mNIS+7 score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurologic impairment (range = 0 to 304). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Alnylam Pharmaceuticals Inc.
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Table 2.8
Modified Neuropathy Impairment Score +7 (mNIS+7) Components: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Component: Postural Blood Pressure (PBP)

Previous Tetramer Stabilizer Use: Yes

Subgroup Visit	Vutrisiran (HELIOS-A) (N=75)	Patisiran (HELIOS-A) (N=33)
Baseline		
n	75	33
Mean (SD)	0.37 (0.63)	0.45 (0.69)
SE	0.07	0.12
Median	0.00	0.00
Min, Max	0.0, 2.0	0.0, 2.0
Month 9		
Actual Value		
n	74	32
Mean (SD)	0.44 (0.74)	0.42 (0.73)
SE	0.09	0.13
Median	0.00	0.00
Min, Max	0.0, 2.0	0.0, 2.0
Change from baseline		
n	74	32
Mean (SD)	0.07 (0.61)	-0.05 (0.69)
SE	0.07	0.12
Median	0.00	0.00
Min, Max	-1.5, 2.0	-2.0, 2.0

mNIS+7 score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurologic impairment (range = 0 to 304). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 2.8
Modified Neuropathy Impairment Score +7 (mNIS+7) Components: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Component: Postural Blood Pressure (PBP)

Previous Tetramer Stabilizer Use: Yes

Subgroup Visit	Vutrisiran (HELIOS-A) (N=75)	Patisiran (HELIOS-A) (N=33)
Month 18		
Actual Value		
n	71	31
Mean (SD)	0.47 (0.71)	0.48 (0.69)
SE	0.08	0.12
Median	0.00	0.00
Min, Max	0.0, 2.0	0.0, 2.0
Change from baseline		
n	71	31
Mean (SD)	0.10 (0.59)	0.00 (0.62)
SE	0.07	0.11
Median	0.00	0.00
Min, Max	-2.0, 1.5	-1.5, 1.5

mNIS+7 score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurologic impairment (range = 0 to 304). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 2.8
Modified Neuropathy Impairment Score +7 (mNIS+7) Components: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Component: Postural Blood Pressure (PBP)

Previous Tetramer Stabilizer Use: No

Subgroup Visit	Vutrisiran (HELIOS-A) (N=47)	Patisiran (HELIOS-A) (N=9)
Baseline		
n	47	9
Mean (SD)	0.34 (0.56)	0.39 (0.78)
SE	0.08	0.26
Median	0.00	0.00
Min, Max	0.0, 2.0	0.0, 2.0
Month 9		
Actual Value		
n	43	8
Mean (SD)	0.24 (0.50)	0.19 (0.37)
SE	0.08	0.13
Median	0.00	0.00
Min, Max	0.0, 2.0	0.0, 1.0
Change from baseline		
n	43	8
Mean (SD)	-0.07 (0.52)	-0.25 (0.46)
SE	0.08	0.16
Median	0.00	0.00
Min, Max	-2.0, 1.0	-1.0, 0.0

mNIS+7 score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurologic impairment (range = 0 to 304). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 2.8
Modified Neuropathy Impairment Score +7 (mNIS+7) Components: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Component: Postural Blood Pressure (PBP)

Previous Tetramer Stabilizer Use: No

Subgroup Visit	Vutrisiran (HELIOS-A) (N=47)	Patisiran (HELIOS-A) (N=9)
Month 18		
Actual Value		
n	44	7
Mean (SD)	0.31 (0.58)	0.57 (0.84)
SE	0.09	0.32
Median	0.00	0.00
Min, Max	0.0, 2.0	0.0, 2.0
Change from baseline		
n	44	7
Mean (SD)	-0.01 (0.70)	0.07 (0.35)
SE	0.11	0.13
Median	0.00	0.00
Min, Max	-2.0, 1.5	-0.5, 0.5

mNIS+7 score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurologic impairment (range = 0 to 304). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 2.8
Modified Neuropathy Impairment Score +7 (mNIS+7) Components: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Component: Postural Blood Pressure (PBP)

Genotype: V30M

Subgroup Visit	Vutrisiran (HELIOS-A) (N=54)	Patisiran (HELIOS-A) (N=20)
Baseline		
n	54	20
Mean (SD)	0.26 (0.42)	0.53 (0.73)
SE	0.06	0.16
Median	0.00	0.00
Min, Max	0.0, 2.0	0.0, 2.0
Month 9		
Actual Value		
n	52	20
Mean (SD)	0.26 (0.56)	0.55 (0.79)
SE	0.08	0.18
Median	0.00	0.00
Min, Max	0.0, 2.0	0.0, 2.0
Change from baseline		
n	52	20
Mean (SD)	0.00 (0.46)	0.03 (0.70)
SE	0.06	0.16
Median	0.00	0.00
Min, Max	-1.0, 1.5	-1.0, 2.0

mNIS+7 score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurologic impairment (range = 0 to 304). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

Alnylam Pharmaceuticals Inc.
ALN-TTRSC02-002

Table 2.8
Modified Neuropathy Impairment Score +7 (mNIS+7) Components: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Component: Postural Blood Pressure (PBP)

Genotype: V30M

Subgroup Visit	Vutrisiran (HELIOS-A) (N=54)	Patisiran (HELIOS-A) (N=20)
Month 18		
Actual Value		
n	52	20
Mean (SD)	0.41 (0.66)	0.58 (0.80)
SE	0.09	0.18
Median	0.00	0.00
Min, Max	0.0, 2.0	0.0, 2.0
Change from baseline		
n	52	20
Mean (SD)	0.16 (0.55)	0.05 (0.58)
SE	0.08	0.13
Median	0.00	0.00
Min, Max	-1.0, 1.5	-1.0, 1.5

mNIS+7 score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurologic impairment (range = 0 to 304). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

Alnylam Pharmaceuticals Inc.
ALN-TTRSC02-002

Table 2.8
Modified Neuropathy Impairment Score +7 (mNIS+7) Components: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Component: Postural Blood Pressure (PBP)

Genotype: non-V30M

Subgroup Visit	Vutrisiran (HELIOS-A) (N=68)	Patisiran (HELIOS-A) (N=22)
Baseline		
n	68	22
Mean (SD)	0.43 (0.71)	0.36 (0.68)
SE	0.09	0.14
Median	0.00	0.00
Min, Max	0.0, 2.0	0.0, 2.0
Month 9		
Actual Value		
n	65	20
Mean (SD)	0.45 (0.74)	0.20 (0.50)
SE	0.09	0.11
Median	0.00	0.00
Min, Max	0.0, 2.0	0.0, 2.0
Change from baseline		
n	65	20
Mean (SD)	0.03 (0.66)	-0.20 (0.59)
SE	0.08	0.13
Median	0.00	0.00
Min, Max	-2.0, 2.0	-2.0, 1.0

mNIS+7 score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurologic impairment (range = 0 to 304). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

Alnylam Pharmaceuticals Inc.
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Table 2.8
Modified Neuropathy Impairment Score +7 (mNIS+7) Components: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Component: Postural Blood Pressure (PBP)

Genotype: non-V30M

Subgroup Visit	Vutrisiran (HELIOS-A) (N=68)	Patisiran (HELIOS-A) (N=22)
Month 18		
Actual Value		
n	63	18
Mean (SD)	0.40 (0.67)	0.42 (0.60)
SE	0.08	0.14
Median	0.00	0.00
Min, Max	0.0, 2.0	0.0, 2.0
Change from baseline		
n	63	18
Mean (SD)	-0.03 (0.69)	-0.03 (0.58)
SE	0.09	0.14
Median	0.00	0.00
Min, Max	-2.0, 1.5	-1.5, 0.5

mNIS+7 score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurologic impairment (range = 0 to 304). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

Alnylam Pharmaceuticals Inc.
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Table 2.8
Modified Neuropathy Impairment Score +7 (mNIS+7) Components: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Component: Postural Blood Pressure (PBP)

FAP Stage: I

Subgroup Visit	Vutrisiran (HELIOS-A) (N=84)	Patisiran (HELIOS-A) (N=31)
Baseline		
n	84	31
Mean (SD)	0.32 (0.58)	0.47 (0.73)
SE	0.06	0.13
Median	0.00	0.00
Min, Max	0.0, 2.0	0.0, 2.0
Month 9		
Actual Value		
n	82	30
Mean (SD)	0.24 (0.53)	0.38 (0.67)
SE	0.06	0.12
Median	0.00	0.00
Min, Max	0.0, 2.0	0.0, 2.0
Change from baseline		
n	82	30
Mean (SD)	-0.05 (0.48)	-0.10 (0.70)
SE	0.05	0.13
Median	0.00	0.00
Min, Max	-2.0, 2.0	-2.0, 2.0

mNIS+7 score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurologic impairment (range = 0 to 304). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

Alnylam Pharmaceuticals Inc.
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Table 2.8
Modified Neuropathy Impairment Score +7 (mNIS+7) Components: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Component: Postural Blood Pressure (PBP)

FAP Stage: I

Subgroup Visit	Vutrisiran (HELIOS-A) (N=84)	Patisiran (HELIOS-A) (N=31)
Month 18		
Actual Value		
n	81	30
Mean (SD)	0.37 (0.66)	0.47 (0.67)
SE	0.07	0.12
Median	0.00	0.00
Min, Max	0.0, 2.0	0.0, 2.0
Change from baseline		
n	81	30
Mean (SD)	0.08 (0.54)	-0.02 (0.53)
SE	0.06	0.10
Median	0.00	0.00
Min, Max	-2.0, 1.5	-1.5, 1.5

mNIS+7 score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurologic impairment (range = 0 to 304). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

Alnylam Pharmaceuticals Inc.
ALN-TTRSC02-002

Table 2.8
Modified Neuropathy Impairment Score +7 (mNIS+7) Components: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Component: Postural Blood Pressure (PBP)

FAP Stage: II&III

Subgroup Visit	Vutrisiran (HELIOS-A) (N=38)	Patisiran (HELIOS-A) (N=11)
Baseline		
n	38	11
Mean (SD)	0.45 (0.65)	0.36 (0.64)
SE	0.10	0.19
Median	0.00	0.00
Min, Max	0.0, 2.0	0.0, 2.0
Month 9		
Actual Value		
n	35	10
Mean (SD)	0.67 (0.85)	0.35 (0.75)
SE	0.14	0.24
Median	0.00	0.00
Min, Max	0.0, 2.0	0.0, 2.0
Change from baseline		
n	35	10
Mean (SD)	0.19 (0.74)	-0.05 (0.50)
SE	0.12	0.16
Median	0.00	0.00
Min, Max	-1.5, 2.0	-1.0, 1.0

mNIS+7 score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurologic impairment (range = 0 to 304). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

Alnylam Pharmaceuticals Inc.
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Table 2.8
Modified Neuropathy Impairment Score +7 (mNIS+7) Components: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Component: Postural Blood Pressure (PBP)

FAP Stage: II&III

Subgroup Visit	Vutrisiran (HELIOS-A) (N=38)	Patisiran (HELIOS-A) (N=11)
Month 18		
Actual Value		
n	34	8
Mean (SD)	0.50 (0.69)	0.63 (0.88)
SE	0.12	0.31
Median	0.00	0.25
Min, Max	0.0, 2.0	0.0, 2.0
Change from baseline		
n	34	8
Mean (SD)	0.00 (0.83)	0.13 (0.74)
SE	0.14	0.26
Median	0.00	0.00
Min, Max	-2.0, 1.5	-1.0, 1.5

mNIS+7 score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurologic impairment (range = 0 to 304). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

Alnylam Pharmaceuticals Inc.
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Table 2.8
Modified Neuropathy Impairment Score +7 (mNIS+7) Components: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Component: Postural Blood Pressure (PBP)

Cardiac Subpopulation: Yes

Subgroup Visit	Vutrisiran (HELIOS-A) (N=40)	Patisiran (HELIOS-A) (N=14)
Baseline		
n	40	14
Mean (SD)	0.65 (0.79)	0.36 (0.60)
SE	0.13	0.16
Median	0.25	0.00
Min, Max	0.0, 2.0	0.0, 2.0
Month 9		
Actual Value		
n	38	14
Mean (SD)	0.78 (0.88)	0.46 (0.80)
SE	0.14	0.21
Median	0.25	0.00
Min, Max	0.0, 2.0	0.0, 2.0
Change from baseline		
n	38	14
Mean (SD)	0.14 (0.76)	0.11 (0.56)
SE	0.12	0.15
Median	0.00	0.00
Min, Max	-1.5, 2.0	-1.0, 1.0

mNIS+7 score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurologic impairment (range = 0 to 304). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

Alnylam Pharmaceuticals Inc.
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Table 2.8
Modified Neuropathy Impairment Score +7 (mNIS+7) Components: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Component: Postural Blood Pressure (PBP)

Cardiac Subpopulation: Yes

Subgroup Visit	Vutrisiran (HELIOS-A) (N=40)	Patisiran (HELIOS-A) (N=14)
Month 18		
Actual Value		
n	37	13
Mean (SD)	0.65 (0.76)	0.46 (0.63)
SE	0.13	0.17
Median	0.50	0.00
Min, Max	0.0, 2.0	0.0, 2.0
Change from baseline		
n	37	13
Mean (SD)	0.00 (0.76)	0.08 (0.64)
SE	0.13	0.18
Median	0.00	0.00
Min, Max	-2.0, 1.5	-1.0, 1.5

mNIS+7 score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurologic impairment (range = 0 to 304). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

Alnylam Pharmaceuticals Inc.
ALN-TTRSC02-002

Table 2.8
Modified Neuropathy Impairment Score +7 (mNIS+7) Components: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Component: Postural Blood Pressure (PBP)

Cardiac Subpopulation: No

Subgroup Visit	Vutrisiran (HELIOS-A) (N=82)	Patisiran (HELIOS-A) (N=28)
Baseline		
n	82	28
Mean (SD)	0.21 (0.42)	0.48 (0.75)
SE	0.05	0.14
Median	0.00	0.00
Min, Max	0.0, 2.0	0.0, 2.0
Month 9		
Actual Value		
n	79	26
Mean (SD)	0.17 (0.43)	0.33 (0.62)
SE	0.05	0.12
Median	0.00	0.00
Min, Max	0.0, 2.0	0.0, 2.0
Change from baseline		
n	79	26
Mean (SD)	-0.04 (0.46)	-0.19 (0.68)
SE	0.05	0.13
Median	0.00	0.00
Min, Max	-2.0, 1.5	-2.0, 2.0

mNIS+7 score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurologic impairment (range = 0 to 304). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

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Table 2.8
Modified Neuropathy Impairment Score +7 (mNIS+7) Components: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Component: Postural Blood Pressure (PBP)

Cardiac Subpopulation: No

Subgroup Visit	Vutrisiran (HELIOS-A) (N=82)	Patisiran (HELIOS-A) (N=28)
Month 18		
Actual Value		
n	78	25
Mean (SD)	0.29 (0.58)	0.52 (0.76)
SE	0.07	0.15
Median	0.00	0.00
Min, Max	0.0, 2.0	0.0, 2.0
Change from baseline		
n	78	25
Mean (SD)	0.08 (0.57)	-0.02 (0.55)
SE	0.06	0.11
Median	0.00	0.00
Min, Max	-2.0, 1.5	-1.5, 1.5

mNIS+7 score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurologic impairment (range = 0 to 304). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

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Table 2.8
Modified Neuropathy Impairment Score +7 (mNIS+7) Components: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Component: Postural Blood Pressure (PBP)

Weight (kg): <65

Subgroup Visit	Vutrisiran (HELIOS-A) (N=46)	Patisiran (HELIOS-A) (N=15)
Baseline		
n	46	15
Mean (SD)	0.57 (0.70)	0.70 (0.90)
SE	0.10	0.23
Median	0.25	0.00
Min, Max	0.0, 2.0	0.0, 2.0
Month 9		
Actual Value		
n	44	15
Mean (SD)	0.53 (0.79)	0.57 (0.80)
SE	0.12	0.21
Median	0.00	0.00
Min, Max	0.0, 2.0	0.0, 2.0
Change from baseline		
n	44	15
Mean (SD)	-0.01 (0.69)	-0.13 (0.90)
SE	0.10	0.23
Median	0.00	0.00
Min, Max	-2.0, 2.0	-2.0, 2.0

mNIS+7 score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurologic impairment (range = 0 to 304). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

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Table 2.8
Modified Neuropathy Impairment Score +7 (mNIS+7) Components: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Component: Postural Blood Pressure (PBP)

Weight (kg): <65

Subgroup Visit	Vutrisiran (HELIOS-A) (N=46)	Patisiran (HELIOS-A) (N=15)
Month 18		
Actual Value		
n	42	15
Mean (SD)	0.56 (0.73)	0.87 (0.88)
SE	0.11	0.23
Median	0.25	0.50
Min, Max	0.0, 2.0	0.0, 2.0
Change from baseline		
n	42	15
Mean (SD)	0.01 (0.78)	0.17 (0.72)
SE	0.12	0.19
Median	0.00	0.00
Min, Max	-2.0, 1.5	-1.5, 1.5

mNIS+7 score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurologic impairment (range = 0 to 304). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

Alnylam Pharmaceuticals Inc.
ALN-TTRSC02-002

Table 2.8
Modified Neuropathy Impairment Score +7 (mNIS+7) Components: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Component: Postural Blood Pressure (PBP)

Weight (kg): ≥65

Subgroup Visit	Vutrisiran (HELIOS-A) (N=76)	Patisiran (HELIOS-A) (N=27)
Baseline		
n	76	27
Mean (SD)	0.23 (0.50)	0.30 (0.52)
SE	0.06	0.10
Median	0.00	0.00
Min, Max	0.0, 2.0	0.0, 2.0
Month 9		
Actual Value		
n	73	25
Mean (SD)	0.27 (0.57)	0.26 (0.58)
SE	0.07	0.12
Median	0.00	0.00
Min, Max	0.0, 2.0	0.0, 2.0
Change from baseline		
n	73	25
Mean (SD)	0.03 (0.51)	-0.06 (0.46)
SE	0.06	0.09
Median	0.00	0.00
Min, Max	-1.5, 2.0	-1.0, 1.0

mNIS+7 score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurologic impairment (range = 0 to 304). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

Alnylam Pharmaceuticals Inc.
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Table 2.8
Modified Neuropathy Impairment Score +7 (mNIS+7) Components: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Component: Postural Blood Pressure (PBP)

Weight (kg): ≥65

Subgroup Visit	Vutrisiran (HELIOS-A) (N=76)	Patisiran (HELIOS-A) (N=27)
Month 18		
Actual Value		
n	73	23
Mean (SD)	0.32 (0.61)	0.26 (0.45)
SE	0.07	0.09
Median	0.00	0.00
Min, Max	0.0, 2.0	0.0, 1.5
Change from baseline		
n	73	23
Mean (SD)	0.08 (0.54)	-0.09 (0.44)
SE	0.06	0.09
Median	0.00	0.00
Min, Max	-2.0, 1.5	-1.0, 0.5

mNIS+7 score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurologic impairment (range = 0 to 304). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Subgruppenanalysen zum Endpunkt „Veränderung der polyneuropathischen Symptomatik gemessen anhand des NIS“

NIS-Gesamtwert (Kontinuierliche Analyse)

Alnylam Pharmaceuticals Inc.
ALN-TTRSC02-002

Table 16.5
Neuropathy Impairment Score (NIS): Change from Baseline to Month 18, MMRM Model
Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A) Subgroup Analysis
mITT Population

Subgroup Visit	LS Mean (95% CI) Vutrisiran (HELIOS-A) (N=122)	LS Mean (95% CI) Patisiran (HELIOS-A) (N=42)	LS Mean Difference (Vutrisiran-Patisiran) (95% CI), p-value	Standardized Effect Size (95% CI)
Age (years)				
<65	75	30		
Month 9	-0.64 (-2.80, 1.52)	-1.09 (-4.50, 2.32)	0.45 (-3.58, 4.47), 0.8269	0.05 (-0.37, 0.47)
Month 18	2.28 (-0.53, 5.10)	1.99 (-2.72, 6.69)	0.30 (-5.18, 5.77), 0.9143	0.02 (-0.42, 0.46)
≥65	44	10		
Month 9	0.43 (-2.40, 3.25)	-0.37 (-6.27, 5.53)	0.80 (-5.72, 7.32), 0.8091	0.07 (-0.60, 0.75)
Month 18	3.35 (0.01, 6.70)	2.70 (-4.02, 9.43)	0.65 (-6.84, 8.15), 0.8639	0.06 (-0.65, 0.77)
p-value of Treatment*Age	0.9276			

NIS score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurological impairment (range = 0 to 244).
LS estimates and p-value derived from mixed-effects model for repeated measures (MMRM), controlling for categorical factors (treatment, visit), the subgroup variable, continuous covariate (baseline value), and interaction (treatment by visit, treatment by subgroup).
Standardized effect size (d) = LS mean difference/estimated pooled standard deviation with the small sample bias correction.

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Table 16.5
Neuropathy Impairment Score (NIS): Change from Baseline to Month 18, MMRM Model
Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A) Subgroup Analysis
mITT Population

Subgroup Visit	LS Mean (95% CI) Vutrisiran (HELIOS-A) (N=122)	LS Mean (95% CI) Patisiran (HELIOS-A) (N=42)	LS Mean Difference (Vutrisiran-Patisiran) (95% CI), p-value	Standardized Effect Size (95% CI)
Sex				
Male	77	25		
Month 9	-0.36 (-2.49, 1.78)	-0.52 (-4.24, 3.20)	0.16 (-4.13, 4.45), 0.9412	0.02 (-0.43, 0.47)
Month 18	2.57 (-0.23, 5.36)	2.56 (-2.38, 7.49)	0.01 (-5.66, 5.68), 0.9973	0.00 (-0.47, 0.47)
Female	42	15		
Month 9	-0.04 (-2.96, 2.87)	-1.55 (-6.35, 3.25)	1.51 (-4.10, 7.11), 0.5957	0.14 (-0.45, 0.72)
Month 18	2.88 (-0.53, 6.30)	1.53 (-4.26, 7.31)	1.36 (-5.35, 8.06), 0.6901	0.09 (-0.51, 0.69)
p-value of Treatment*Sex	0.7062			

NIS score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurological impairment (range = 0 to 244).
LS estimates and p-value derived from mixed-effects model for repeated measures (MMRM), controlling for categorical factors (treatment, visit), the subgroup variable, continuous covariate (baseline value), and interaction (treatment by visit, treatment by subgroup).
Standardized effect size (d) = LS mean difference/estimated pooled standard deviation with the small sample bias correction.

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Table 16.5
Neuropathy Impairment Score (NIS): Change from Baseline to Month 18, MMRM Model
Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A) Subgroup Analysis
mITT Population

Subgroup Visit	LS Mean (95% CI) Vutrisiran (HELIOS-A) (N=122)	LS Mean (95% CI) Patisiran (HELIOS-A) (N=42)	LS Mean Difference (Vutrisiran-Patisiran) (95% CI), p-value	Standardized Effect Size (95% CI)
Race				
White	84	28		
Month 9	-1.30 (-3.31, 0.71)	-0.01 (-3.48, 3.45)	-1.28 (-5.29, 2.72), 0.5277	-0.14 (-0.56, 0.29)
Month 18	1.62 (-1.08, 4.32)	3.06 (-1.69, 7.81)	-1.44 (-6.90, 4.03), 0.6042	-0.10 (-0.55, 0.34)
All Other Races	35	12		
Month 9	2.29 (-0.83, 5.42)	-3.00 (-8.29, 2.30)	5.29 (-0.86, 11.44), 0.0911	0.56 (-0.09, 1.22)
Month 18	5.22 (1.62, 8.81)	0.08 (-6.12, 6.28)	5.14 (-2.03, 12.31), 0.1593	0.39 (-0.29, 1.06)
p-value of Treatment*Race	0.0784			

NIS score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurological impairment (range = 0 to 244).
LS estimates and p-value derived from mixed-effects model for repeated measures (MMRM), controlling for categorical factors (treatment, visit), the subgroup variable, continuous covariate (baseline value), and interaction (treatment by visit, treatment by subgroup).
Standardized effect size (d) = LS mean difference/estimated pooled standard deviation with the small sample bias correction.

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Table 16.5
Neuropathy Impairment Score (NIS): Change from Baseline to Month 18, MMRM Model
Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A) Subgroup Analysis
mITT Population

Subgroup Visit	LS Mean (95% CI) Vutrisiran (HELIOS-A) (N=122)	LS Mean (95% CI) Patisiran (HELIOS-A) (N=42)	LS Mean Difference (Vutrisiran-Patisiran) (95% CI), p-value	Standardized Effect Size (95% CI)
Region				
North America	27	8		
Month 9	-2.33 (-6.15, 1.49)	-2.00 (-8.60, 4.59)	-0.33 (-7.82, 7.16), 0.9311	-0.04 (-0.82, 0.73)
Month 18	0.61 (-3.57, 4.80)	1.07 (-6.29, 8.42)	-0.46 (-8.80, 7.89), 0.9145	-0.04 (-0.91, 0.82)
Western Europe	40	18		
Month 9	0.94 (-1.99, 3.86)	-2.44 (-6.80, 1.93)	3.37 (-1.88, 8.63), 0.2069	0.33 (-0.22, 0.89)
Month 18	3.88 (0.45, 7.31)	0.64 (-4.78, 6.06)	3.24 (-3.17, 9.66), 0.3199	0.36 (-0.20, 0.93)
Rest of World	52	14		
Month 9	-0.14 (-2.75, 2.48)	1.64 (-3.30, 6.59)	-1.78 (-7.37, 3.81), 0.5302	-0.19 (-0.77, 0.40)
Month 18	2.81 (-0.37, 5.99)	4.72 (-1.18, 10.62)	-1.91 (-8.60, 4.79), 0.5753	-0.11 (-0.71, 0.50)
p-value of Treatment*Region	0.3976			

NIS score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurological impairment (range = 0 to 244).
LS estimates and p-value derived from mixed-effects model for repeated measures (MMRM), controlling for categorical factors (treatment, visit), the subgroup variable, continuous covariate (baseline value), and interaction (treatment by visit, treatment by subgroup).
Standardized effect size (d) = LS mean difference/estimated pooled standard deviation with the small sample bias correction.

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Table 16.5
Neuropathy Impairment Score (NIS): Change from Baseline to Month 18, MMRM Model
Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A) Subgroup Analysis
mITT Population

Subgroup Visit	LS Mean (95% CI) Vutrisiran (HELIOS-A) (N=122)	LS Mean (95% CI) Patisiran (HELIOS-A) (N=42)	LS Mean Difference (Vutrisiran-Patisiran) (95% CI), p-value	Standardized Effect Size (95% CI)
Baseline NIS				
<50	77	27		
Month 9	-1.41 (-4.25, 1.44)	-2.87 (-6.85, 1.11)	1.46 (-2.68, 5.60), 0.4865	0.19 (-0.25, 0.62)
Month 18	1.52 (-1.86, 4.89)	0.21 (-4.92, 5.34)	1.31 (-4.26, 6.87), 0.6438	0.11 (-0.34, 0.56)
≥50	42	13		
Month 9	1.83 (-2.64, 6.30)	2.92 (-3.15, 8.98)	-1.08 (-6.96, 4.80), 0.7168	-0.09 (-0.71, 0.53)
Month 18	4.76 (-0.04, 9.56)	5.99 (-0.88, 12.86)	-1.24 (-8.18, 5.71), 0.7262	-0.07 (-0.73, 0.59)
p-value of Treatment*Baseline NIS	0.4855			

NIS score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurological impairment (range = 0 to 244).
LS estimates and p-value derived from mixed-effects model for repeated measures (MMRM), controlling for categorical factors (treatment, visit), the subgroup variable, continuous covariate (baseline value), and interaction (treatment by visit, treatment by subgroup).
Standardized effect size (d) = LS mean difference/estimated pooled standard deviation with the small sample bias correction.

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Table 16.5
Neuropathy Impairment Score (NIS): Change from Baseline to Month 18, MMRM Model
Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A) Subgroup Analysis
mITT Population

Subgroup Visit	LS Mean (95% CI) Vutrisiran (HELIOS-A) (N=122)	LS Mean (95% CI) Patisiran (HELIOS-A) (N=42)	LS Mean Difference (Vutrisiran-Patisiran) (95% CI), p-value	Standardized Effect Size (95% CI)
Previous Tetramer Stabilizer Use				
Yes	74	32		
Month 9	-0.82 (-2.98, 1.33)	-0.36 (-3.63, 2.92)	-0.47 (-4.39, 3.45), 0.8139	-0.05 (-0.46, 0.36)
Month 18	2.09 (-0.73, 4.91)	2.72 (-1.89, 7.33)	-0.63 (-6.03, 4.78), 0.8192	-0.04 (-0.47, 0.39)
No	45	8		
Month 9	0.73 (-2.08, 3.54)	-3.10 (-9.68, 3.47)	3.83 (-3.29, 10.95), 0.2899	0.39 (-0.35, 1.14)
Month 18	3.64 (0.33, 6.96)	-0.03 (-7.35, 7.30)	3.67 (-4.35, 11.69), 0.3677	0.34 (-0.45, 1.13)
p-value of Treatment*Previous Tetramer Stabilizer Use	0.2975			

NIS score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurological impairment (range = 0 to 244).
LS estimates and p-value derived from mixed-effects model for repeated measures (MMRM), controlling for categorical factors (treatment, visit), the subgroup variable, continuous covariate (baseline value), and interaction (treatment by visit, treatment by subgroup).
Standardized effect size (d) = LS mean difference/estimated pooled standard deviation with the small sample bias correction.

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Table 16.5
Neuropathy Impairment Score (NIS): Change from Baseline to Month 18, MMRM Model
Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A) Subgroup Analysis
mITT Population

Subgroup Visit	LS Mean (95% CI) Vutrisiran (HELIOS-A) (N=122)	LS Mean (95% CI) Patisiran (HELIOS-A) (N=42)	LS Mean Difference (Vutrisiran-Patisiran) (95% CI), p-value	Standardized Effect Size (95% CI)
Genotype				
V30M	53	20		
Month 9	0.19 (-2.36, 2.73)	-3.22 (-7.36, 0.91)	3.41 (-1.44, 8.27), 0.1668	0.42 (-0.09, 0.94)
Month 18	3.11 (0.00, 6.22)	-0.13 (-5.37, 5.10)	3.25 (-2.84, 9.33), 0.2943	0.33 (-0.19, 0.85)
non-V30M	66	20		
Month 9	-0.59 (-2.87, 1.69)	1.43 (-2.72, 5.57)	-2.02 (-6.74, 2.71), 0.4006	-0.19 (-0.69, 0.30)
Month 18	2.33 (-0.57, 5.23)	4.52 (-0.74, 9.78)	-2.18 (-8.19, 3.82), 0.4744	-0.13 (-0.66, 0.40)
p-value of Treatment*Genotype	0.1154			

NIS score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurological impairment (range = 0 to 244).
LS estimates and p-value derived from mixed-effects model for repeated measures (MMRM), controlling for categorical factors (treatment, visit), the subgroup variable, continuous covariate (baseline value), and interaction (treatment by visit, treatment by subgroup).
Standardized effect size (d) = LS mean difference/estimated pooled standard deviation with the small sample bias correction.

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Table 16.5
Neuropathy Impairment Score (NIS): Change from Baseline to Month 18, MMRM Model
Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A) Subgroup Analysis
mITT Population

Subgroup Visit	LS Mean (95% CI) Vutrisiran (HELIOS-A) (N=122)	LS Mean (95% CI) Patisiran (HELIOS-A) (N=42)	LS Mean Difference (Vutrisiran-Patisiran) (95% CI), p-value	Standardized Effect Size (95% CI)
FAP Stage				
I	83	30		
Month 9	-0.94 (-3.13, 1.25)	-0.65 (-4.12, 2.83)	-0.30 (-4.25, 3.66), 0.8828	-0.03 (-0.45, 0.38)
Month 18	1.99 (-0.84, 4.82)	2.42 (-2.33, 7.17)	-0.43 (-5.85, 4.98), 0.8744	-0.03 (-0.45, 0.39)
II&III	36	10		
Month 9	1.34 (-2.20, 4.87)	-1.77 (-7.97, 4.42)	3.11 (-3.53, 9.74), 0.3565	0.30 (-0.39, 1.00)
Month 18	4.26 (0.30, 8.23)	1.30 (-5.71, 8.30)	2.97 (-4.65, 10.58), 0.4432	0.24 (-0.56, 1.04)
p-value of Treatment*FAP Stage	0.3852			

NIS score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurological impairment (range = 0 to 244).
LS estimates and p-value derived from mixed-effects model for repeated measures (MMRM), controlling for categorical factors (treatment, visit), the subgroup variable, continuous covariate (baseline value), and interaction (treatment by visit, treatment by subgroup).
Standardized effect size (d) = LS mean difference/estimated pooled standard deviation with the small sample bias correction.

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Table 16.5
Neuropathy Impairment Score (NIS): Change from Baseline to Month 18, MMRM Model
Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A) Subgroup Analysis
mITT Population

Subgroup Visit	LS Mean (95% CI) Vutrisiran (HELIOS-A) (N=122)	LS Mean (95% CI) Patisiran (HELIOS-A) (N=42)	LS Mean Difference (Vutrisiran-Patisiran) (95% CI), p-value	Standardized Effect Size (95% CI)
Cardiac Subpopulation				
Yes	38	14		
Month 9	-0.48 (-3.36, 2.40)	8.27 (3.62, 12.92)	-8.75 (-14.16, -3.33), 0.0017	-0.91 (-1.54, -0.28)
Month 18	2.45 (-0.98, 5.89)	11.32 (5.60, 17.03)	-8.86 (-15.48, -2.24), 0.0089	-0.47 (-1.10, 0.16)
No	81	26		
Month 9	-0.15 (-2.12, 1.82)	-5.88 (-9.30, -2.47)	5.73 (1.82, 9.64), 0.0043	0.68 (0.23, 1.13)
Month 18	2.78 (0.08, 5.48)	-2.84 (-7.61, 1.94)	5.61 (0.15, 11.08), 0.0441	0.56 (0.09, 1.03)
p-value of Treatment*Cardiac Subpopulation	3.223E-05			

NIS score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurological impairment (range = 0 to 244).
LS estimates and p-value derived from mixed-effects model for repeated measures (MMRM), controlling for categorical factors (treatment, visit), the subgroup variable, continuous covariate (baseline value), and interaction (treatment by visit, treatment by subgroup).
Standardized effect size (d) = LS mean difference/estimated pooled standard deviation with the small sample bias correction.

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Table 16.5
Neuropathy Impairment Score (NIS): Change from Baseline to Month 18, MMRM Model
Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A) Subgroup Analysis
mITT Population

Subgroup Visit	LS Mean (95% CI) Vutrisiran (HELIOS-A) (N=122)	LS Mean (95% CI) Patisiran (HELIOS-A) (N=42)	LS Mean Difference (Vutrisiran-Patisiran) (95% CI), p-value	Standardized Effect Size (95% CI)
Weight (kg)				
<65	44	15		
Month 9	-0.00 (-2.84, 2.83)	-1.10 (-5.90, 3.70)	1.10 (-4.49, 6.68), 0.6983	0.11 (-0.47, 0.68)
Month 18	2.93 (-0.44, 6.29)	1.97 (-3.82, 7.76)	0.95 (-5.75, 7.66), 0.7800	0.06 (-0.56, 0.67)
≥65	75	25		
Month 9	-0.39 (-2.58, 1.79)	-0.79 (-4.51, 2.93)	0.40 (-3.91, 4.71), 0.8555	0.04 (-0.41, 0.50)
Month 18	2.53 (-0.29, 5.36)	2.28 (-2.65, 7.21)	0.25 (-5.43, 5.93), 0.9304	0.02 (-0.44, 0.49)
p-value of Treatment*Weight	0.8451			

NIS score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurological impairment (range = 0 to 244).
LS estimates and p-value derived from mixed-effects model for repeated measures (MMRM), controlling for categorical factors (treatment, visit), the subgroup variable, continuous covariate (baseline value), and interaction (treatment by visit, treatment by subgroup).
Standardized effect size (d) = LS mean difference/estimated pooled standard deviation with the small sample bias correction.

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Table 16.7
Neuropathy Impairment Score (NIS): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Age (years): <65

Subgroup Visit	Vutrisiran (HELIOS-A) (N=76)	Patisiran (HELIOS-A) (N=31)
Baseline		
n	76	31
Mean (SD)	40.09 (28.41)	38.16 (24.42)
SE	3.26	4.39
Median	33.56	33.00
Min, Max	5.0, 127.0	5.5, 89.4
Month 9		
Actual Value		
n	74	30
Mean (SD)	38.99 (28.91)	36.34 (26.48)
SE	3.36	4.83
Median	29.50	30.50
Min, Max	3.0, 132.6	2.0, 100.3
Change from baseline		
n	74	30
Mean (SD)	-0.55 (7.26)	-0.89 (11.33)
SE	0.84	2.07
Median	0.00	-2.00
Min, Max	-20.4, 16.0	-21.0, 43.9

NIS score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurological impairment (range = 0 to 244).

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Table 16.7
Neuropathy Impairment Score (NIS): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Age (years): <65

Subgroup Visit	Vutrisiran (HELIOS-A) (N=76)	Patisiran (HELIOS-A) (N=31)
Month 18		
Actual Value		
n	74	27
Mean (SD)	41.97 (32.35)	37.70 (32.05)
SE	3.76	6.17
Median	30.88	28.50
Min, Max	0.0, 151.3	3.5, 134.4
Change from baseline		
n	74	27
Mean (SD)	2.58 (12.42)	2.94 (19.62)
SE	1.44	3.78
Median	1.00	2.00
Min, Max	-21.0, 67.5	-38.5, 81.1

NIS score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurological impairment (range = 0 to 244).

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Table 16.7
Neuropathy Impairment Score (NIS): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Age (years): ≥65

Subgroup Visit	Vutrisiran (HELIOS-A) (N=46)	Patisiran (HELIOS-A) (N=11)
Baseline		
n	46	11
Mean (SD)	47.86 (28.65)	57.05 (34.48)
SE	4.22	10.39
Median	45.19	49.00
Min, Max	8.0, 115.9	8.0, 115.6
Month 9		
Actual Value		
n	43	10
Mean (SD)	47.02 (28.36)	53.79 (36.81)
SE	4.33	11.64
Median	44.75	46.25
Min, Max	3.5, 97.1	11.5, 130.0
Change from baseline		
n	43	10
Mean (SD)	0.36 (9.28)	-0.76 (16.87)
SE	1.42	5.33
Median	0.50	4.50
Min, Max	-18.8, 33.0	-27.0, 18.0

NIS score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurological impairment (range = 0 to 244).

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Table 16.7
Neuropathy Impairment Score (NIS): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Age (years): ≥65

Subgroup Visit	Vutrisiran (HELIOS-A) (N=46)	Patisiran (HELIOS-A) (N=11)
Month 18		
Actual Value		
n	41	9
Mean (SD)	50.61 (31.57)	58.72 (32.84)
SE	4.93	10.95
Median	47.00	56.00
Min, Max	6.0, 121.9	12.0, 120.5
Change from baseline		
n	41	9
Mean (SD)	2.70 (10.91)	2.28 (11.83)
SE	1.70	3.94
Median	1.63	4.00
Min, Max	-22.0, 30.5	-18.9, 23.0

NIS score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurological impairment (range = 0 to 244).

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Table 16.7
Neuropathy Impairment Score (NIS): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Sex: Male

Subgroup Visit	Vutrisiran (HELIOS-A) (N=79)	Patisiran (HELIOS-A) (N=27)
Baseline		
n	79	27
Mean (SD)	46.93 (29.22)	45.10 (26.67)
SE	3.29	5.13
Median	39.00	37.50
Min, Max	5.0, 127.0	8.0, 102.9
Month 9		
Actual Value		
n	76	25
Mean (SD)	45.75 (30.48)	42.34 (26.48)
SE	3.50	5.30
Median	37.25	34.00
Min, Max	3.5, 132.6	2.0, 100.3
Change from baseline		
n	76	25
Mean (SD)	-0.48 (7.82)	-0.45 (10.07)
SE	0.90	2.01
Median	0.00	-0.50
Min, Max	-20.4, 16.0	-27.0, 18.0

NIS score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurological impairment (range = 0 to 244).

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Table 16.7
Neuropathy Impairment Score (NIS): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Sex: Male

Subgroup Visit	Vutrisiran (HELIOS-A) (N=79)	Patisiran (HELIOS-A) (N=27)
Month 18		
Actual Value		
n	74	22
Mean (SD)	48.47 (33.62)	42.55 (27.33)
SE	3.91	5.83
Median	39.06	34.81
Min, Max	0.0, 151.3	3.5, 119.4
Change from baseline		
n	74	22
Mean (SD)	2.43 (13.23)	2.52 (9.90)
SE	1.54	2.11
Median	1.50	1.50
Min, Max	-22.0, 67.5	-18.9, 30.0

NIS score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurological impairment (range = 0 to 244).

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Table 16.7
Neuropathy Impairment Score (NIS): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Sex: Female

Subgroup Visit	Vutrisiran (HELIOS-A) (N=43)	Patisiran (HELIOS-A) (N=15)
Baseline		
n	43	15
Mean (SD)	35.82 (26.36)	39.52 (31.48)
SE	4.02	8.13
Median	29.50	38.50
Min, Max	5.5, 115.9	5.5, 115.6
Month 9		
Actual Value		
n	41	15
Mean (SD)	34.89 (24.36)	37.98 (35.67)
SE	3.80	9.21
Median	31.50	25.00
Min, Max	3.0, 97.1	6.0, 130.0
Change from baseline		
n	41	15
Mean (SD)	0.27 (8.49)	-1.54 (16.56)
SE	1.33	4.28
Median	0.00	-2.00
Min, Max	-18.8, 33.0	-26.0, 43.9

NIS score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurological impairment (range = 0 to 244).

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Table 16.7
Neuropathy Impairment Score (NIS): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Sex: Female

Subgroup Visit	Vutrisiran (HELIOS-A) (N=43)	Patisiran (HELIOS-A) (N=15)
Month 18		
Actual Value		
n	41	14
Mean (SD)	38.88 (28.84)	43.59 (41.71)
SE	4.50	11.15
Median	31.75	23.75
Min, Max	0.0, 121.9	9.0, 134.4
Change from baseline		
n	41	14
Mean (SD)	2.96 (9.01)	3.18 (26.41)
SE	1.41	7.06
Median	0.00	2.81
Min, Max	-13.0, 30.5	-38.5, 81.1

NIS score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurological impairment (range = 0 to 244).

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

Alnylam Pharmaceuticals Inc.
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Table 16.7
Neuropathy Impairment Score (NIS): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Race: White

Subgroup Visit	Vutrisiran (HELIOS-A) (N=86)	Patisiran (HELIOS-A) (N=29)
Baseline		
n	86	29
Mean (SD)	42.75 (27.85)	44.57 (27.71)
SE	3.00	5.15
Median	35.50	38.50
Min, Max	5.0, 115.9	5.5, 115.6
Month 9		
Actual Value		
n	83	28
Mean (SD)	40.67 (27.87)	43.13 (30.86)
SE	3.06	5.83
Median	35.50	32.75
Min, Max	3.0, 97.1	6.0, 130.0
Change from baseline		
n	83	28
Mean (SD)	-1.28 (7.04)	-0.11 (14.05)
SE	0.77	2.65
Median	-0.50	1.44
Min, Max	-20.4, 16.0	-27.0, 43.9

NIS score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurological impairment (range = 0 to 244).

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Alnylam Pharmaceuticals Inc.
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Table 16.7
Neuropathy Impairment Score (NIS): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Race: White

Subgroup Visit	Vutrisiran (HELIOS-A) (N=86)	Patisiran (HELIOS-A) (N=29)
Month 18		
Actual Value		
n	82	25
Mean (SD)	44.17 (30.58)	46.38 (34.74)
SE	3.38	6.95
Median	36.75	34.13
Min, Max	0.0, 121.9	9.0, 134.4
Change from baseline		
n	82	25
Mean (SD)	2.12 (11.64)	5.10 (18.93)
SE	1.29	3.79
Median	0.50	2.50
Min, Max	-21.0, 67.5	-24.5, 81.1

NIS score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurological impairment (range = 0 to 244).

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Alnylam Pharmaceuticals Inc.
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Table 16.7
Neuropathy Impairment Score (NIS): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Race: All Other Races

Subgroup Visit	Vutrisiran (HELIOS-A) (N=36)	Patisiran (HELIOS-A) (N=13)
Baseline		
n	36	13
Mean (SD)	43.65 (30.84)	39.85 (30.23)
SE	5.14	8.38
Median	37.75	37.50
Min, Max	5.5, 127.0	8.0, 102.9
Month 9		
Actual Value		
n	34	12
Mean (SD)	45.05 (31.34)	35.05 (27.89)
SE	5.37	8.05
Median	34.25	36.19
Min, Max	8.0, 132.6	2.0, 87.5
Change from baseline		
n	34	12
Mean (SD)	2.38 (9.68)	-2.60 (9.07)
SE	1.66	2.62
Median	2.25	-3.25
Min, Max	-15.0, 33.0	-15.4, 16.5

NIS score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurological impairment (range = 0 to 244).

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

Alnylam Pharmaceuticals Inc.
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Table 16.7
Neuropathy Impairment Score (NIS): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Race: All Other Races

Subgroup Visit	Vutrisiran (HELIOS-A) (N=36)	Patisiran (HELIOS-A) (N=13)
Month 18		
Actual Value		
n	33	11
Mean (SD)	47.23 (36.34)	35.17 (28.97)
SE	6.33	8.73
Median	39.00	20.50
Min, Max	3.0, 151.3	3.5, 84.0
Change from baseline		
n	33	11
Mean (SD)	3.86 (12.47)	-2.50 (14.45)
SE	2.17	4.36
Median	1.50	1.00
Min, Max	-22.0, 30.6	-38.5, 12.5

NIS score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurological impairment (range = 0 to 244).

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Table 16.7
Neuropathy Impairment Score (NIS): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Region: North America

Subgroup Visit	Vutrisiran (HELIOS-A) (N=27)	Patisiran (HELIOS-A) (N=8)
Baseline		
n	27	8
Mean (SD)	23.73 (17.73)	28.00 (14.71)
SE	3.41	5.20
Median	17.50	28.75
Min, Max	5.0, 73.0	5.5, 49.0
Month 9		
Actual Value		
n	25	8
Mean (SD)	18.49 (12.63)	26.86 (18.05)
SE	2.53	6.38
Median	16.00	24.25
Min, Max	3.0, 52.5	6.0, 65.5
Change from baseline		
n	25	8
Mean (SD)	-1.32 (6.57)	-1.14 (10.44)
SE	1.31	3.69
Median	-0.88	-0.75
Min, Max	-13.5, 13.0	-21.0, 16.5

NIS score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurological impairment (range = 0 to 244).

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Alnylam Pharmaceuticals Inc.
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Table 16.7
Neuropathy Impairment Score (NIS): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Region: North America

Subgroup Visit	Vutrisiran (HELIOS-A) (N=27)	Patisiran (HELIOS-A) (N=8)
Month 18		
Actual Value		
n	25	6
Mean (SD)	24.35 (22.17)	25.63 (17.94)
SE	4.43	7.32
Median	16.00	21.50
Min, Max	0.0, 77.0	9.0, 59.3
Change from baseline		
n	25	6
Mean (SD)	0.44 (9.66)	-0.96 (12.66)
SE	1.93	5.17
Median	-0.50	1.00
Min, Max	-17.5, 23.0	-24.5, 10.3

NIS score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurological impairment (range = 0 to 244).

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Table 16.7
Neuropathy Impairment Score (NIS): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Region: Western Europe

Subgroup Visit	Vutrisiran (HELIOS-A) (N=42)	Patisiran (HELIOS-A) (N=20)
Baseline		
n	42	20
Mean (SD)	44.40 (27.48)	47.90 (27.84)
SE	4.24	6.23
Median	36.50	38.63
Min, Max	8.0, 115.9	8.0, 115.6
Month 9		
Actual Value		
n	40	18
Mean (SD)	44.41 (25.57)	42.42 (28.94)
SE	4.04	6.82
Median	39.69	34.25
Min, Max	7.0, 97.1	11.5, 130.0
Change from baseline		
n	40	18
Mean (SD)	0.85 (8.92)	-2.58 (12.99)
SE	1.41	3.06
Median	-0.50	1.88
Min, Max	-18.8, 33.0	-27.0, 18.0

NIS score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurological impairment (range = 0 to 244).

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Table 16.7
Neuropathy Impairment Score (NIS): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Region: Western Europe

Subgroup Visit	Vutrisiran (HELIOS-A) (N=42)	Patisiran (HELIOS-A) (N=20)
Month 18		
Actual Value		
n	40	17
Mean (SD)	48.23 (28.10)	44.86 (26.86)
SE	4.44	6.51
Median	42.19	35.50
Min, Max	10.0, 121.9	12.0, 120.5
Change from baseline		
n	40	17
Mean (SD)	4.67 (9.35)	2.01 (7.80)
SE	1.48	1.89
Median	2.31	2.50
Min, Max	-18.1, 30.5	-14.5, 23.0

NIS score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurological impairment (range = 0 to 244).

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Table 16.7
Neuropathy Impairment Score (NIS): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Region: Rest of World

Subgroup Visit	Vutrisiran (HELIOS-A) (N=53)	Patisiran (HELIOS-A) (N=14)
Baseline		
n	53	14
Mean (SD)	51.75 (29.71)	44.89 (32.93)
SE	4.08	8.80
Median	51.25	45.44
Min, Max	5.5, 127.0	8.0, 102.9
Month 9		
Actual Value		
n	52	14
Mean (SD)	51.32 (30.89)	46.41 (35.36)
SE	4.28	9.45
Median	51.50	44.63
Min, Max	8.0, 132.6	2.0, 100.3
Change from baseline		
n	52	14
Mean (SD)	-0.50 (8.00)	1.52 (13.93)
SE	1.11	3.72
Median	1.00	-2.13
Min, Max	-20.4, 16.0	-15.4, 43.9

NIS score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurological impairment (range = 0 to 244).

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Table 16.7
Neuropathy Impairment Score (NIS): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Region: Rest of World

Subgroup Visit	Vutrisiran (HELIOS-A) (N=53)	Patisiran (HELIOS-A) (N=14)
Month 18		
Actual Value		
n	50	13
Mean (SD)	52.86 (35.42)	48.46 (43.68)
SE	5.01	12.12
Median	57.25	34.00
Min, Max	3.0, 151.3	3.5, 134.4
Change from baseline		
n	50	13
Mean (SD)	2.07 (14.34)	5.50 (27.64)
SE	2.03	7.66
Median	-0.44	1.00
Min, Max	-22.0, 67.5	-38.5, 81.1

NIS score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurological impairment (range = 0 to 244).

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Table 16.7
Neuropathy Impairment Score (NIS): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Baseline NIS: <50

Subgroup Visit	Vutrisiran (HELIOS-A) (N=78)	Patisiran (HELIOS-A) (N=27)
Baseline		
n	78	27
Mean (SD)	24.50 (12.66)	25.47 (13.05)
SE	1.43	2.51
Median	22.00	28.00
Min, Max	5.0, 49.8	5.5, 49.0
Month 9		
Actual Value		
n	77	27
Mean (SD)	24.54 (13.79)	24.18 (14.86)
SE	1.57	2.86
Median	24.00	24.13
Min, Max	3.0, 53.5	2.0, 65.5
Change from baseline		
n	77	27
Mean (SD)	0.35 (7.38)	-1.29 (9.17)
SE	0.84	1.76
Median	0.00	0.00
Min, Max	-18.5, 33.0	-27.0, 16.5

NIS score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurological impairment (range = 0 to 244).

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Table 16.7
Neuropathy Impairment Score (NIS): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Baseline NIS: <50

Subgroup Visit	Vutrisiran (HELIOS-A) (N=78)	Patisiran (HELIOS-A) (N=27)
Month 18		
Actual Value		
n	75	25
Mean (SD)	26.23 (17.50)	26.59 (13.76)
SE	2.02	2.75
Median	24.00	28.00
Min, Max	0.0, 93.5	3.5, 59.3
Change from baseline		
n	75	25
Mean (SD)	1.97 (12.06)	1.67 (9.03)
SE	1.39	1.81
Median	0.50	2.50
Min, Max	-22.0, 67.5	-24.5, 23.0

NIS score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurological impairment (range = 0 to 244).

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Table 16.7
Neuropathy Impairment Score (NIS): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Baseline NIS: ≥50

Subgroup Visit	Vutrisiran (HELIOS-A) (N=44)	Patisiran (HELIOS-A) (N=15)
Baseline		
n	44	15
Mean (SD)	75.85 (17.17)	74.86 (18.37)
SE	2.59	4.74
Median	73.31	70.00
Min, Max	50.5, 127.0	51.5, 115.6
Month 9		
Actual Value		
n	40	13
Mean (SD)	75.44 (18.89)	75.02 (23.08)
SE	2.99	6.40
Median	75.81	67.75
Min, Max	45.0, 132.6	48.5, 130.0
Change from baseline		
n	40	13
Mean (SD)	-1.31 (9.16)	0.04 (18.45)
SE	1.45	5.12
Median	0.94	-3.00
Min, Max	-20.4, 16.0	-26.0, 43.9

NIS score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurological impairment (range = 0 to 244).

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Table 16.7
Neuropathy Impairment Score (NIS): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Baseline NIS: ≥50

Subgroup Visit	Vutrisiran (HELIOS-A) (N=44)	Patisiran (HELIOS-A) (N=15)
Month 18		
Actual Value		
n	40	11
Mean (SD)	80.34 (22.17)	80.14 (34.45)
SE	3.51	10.39
Median	74.25	74.38
Min, Max	46.9, 151.3	13.0, 134.4
Change from baseline		
n	40	11
Mean (SD)	3.84 (11.52)	5.30 (30.11)
SE	1.82	9.08
Median	4.25	1.00
Min, Max	-19.5, 30.6	-38.5, 81.1

NIS score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurological impairment (range = 0 to 244).

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Table 16.7
Neuropathy Impairment Score (NIS): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Previous Tetramer Stabilizer Use: Yes

Subgroup Visit	Vutrisiran (HELIOS-A) (N=75)	Patisiran (HELIOS-A) (N=33)
Baseline		
n	75	33
Mean (SD)	45.58 (30.38)	45.02 (29.78)
SE	3.51	5.18
Median	36.50	38.50
Min, Max	9.0, 127.0	5.5, 115.6
Month 9		
Actual Value		
n	74	32
Mean (SD)	44.39 (31.18)	43.91 (31.32)
SE	3.62	5.54
Median	36.00	36.63
Min, Max	3.0, 132.6	6.0, 130.0
Change from baseline		
n	74	32
Mean (SD)	-0.95 (6.81)	-0.45 (13.33)
SE	0.79	2.36
Median	-1.00	-0.25
Min, Max	-18.8, 16.0	-27.0, 43.9

NIS score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurological impairment (range = 0 to 244).

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Table 16.7
Neuropathy Impairment Score (NIS): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Previous Tetramer Stabilizer Use: Yes

Subgroup Visit	Vutrisiran (HELIOS-A) (N=75)	Patisiran (HELIOS-A) (N=33)
Month 18		
Actual Value		
n	71	29
Mean (SD)	47.44 (34.19)	46.85 (34.76)
SE	4.06	6.46
Median	36.50	34.13
Min, Max	0.0, 151.3	9.0, 134.4
Change from baseline		
n	71	29
Mean (SD)	2.70 (12.76)	4.06 (19.06)
SE	1.51	3.54
Median	0.50	2.50
Min, Max	-22.0, 67.5	-38.5, 81.1

NIS score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurological impairment (range = 0 to 244).

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Table 16.7
Neuropathy Impairment Score (NIS): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Previous Tetramer Stabilizer Use: No

Subgroup Visit	Vutrisiran (HELIOS-A) (N=47)	Patisiran (HELIOS-A) (N=9)
Baseline		
n	47	9
Mean (SD)	38.93 (25.38)	36.10 (21.58)
SE	3.70	7.19
Median	34.50	37.50
Min, Max	5.0, 88.9	8.0, 82.0
Month 9		
Actual Value		
n	43	8
Mean (SD)	37.73 (24.10)	27.89 (19.83)
SE	3.68	7.01
Median	34.50	27.50
Min, Max	3.5, 96.3	2.0, 65.5
Change from baseline		
n	43	8
Mean (SD)	1.05 (9.74)	-2.47 (10.38)
SE	1.49	3.67
Median	1.00	-3.75
Min, Max	-20.4, 33.0	-21.0, 16.5

NIS score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurological impairment (range = 0 to 244).

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Table 16.7
Neuropathy Impairment Score (NIS): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Previous Tetramer Stabilizer Use: No

Subgroup Visit	Vutrisiran (HELIOS-A) (N=47)	Patisiran (HELIOS-A) (N=9)
Month 18		
Actual Value		
n	44	7
Mean (SD)	41.20 (28.67)	26.80 (19.17)
SE	4.32	7.24
Median	39.00	25.00
Min, Max	3.0, 108.1	3.5, 59.3
Change from baseline		
n	44	7
Mean (SD)	2.50 (10.37)	-2.54 (10.85)
SE	1.56	4.10
Median	1.56	-1.50
Min, Max	-21.0, 30.5	-24.5, 10.3

NIS score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurological impairment (range = 0 to 244).

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Table 16.7
Neuropathy Impairment Score (NIS): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Genotype: V30M

Subgroup Visit	Vutrisiran (HELIOS-A) (N=54)	Patisiran (HELIOS-A) (N=20)
Baseline		
n	54	20
Mean (SD)	43.80 (28.14)	47.76 (29.11)
SE	3.83	6.51
Median	40.25	38.63
Min, Max	5.0, 105.4	8.0, 115.6
Month 9		
Actual Value		
n	52	20
Mean (SD)	43.04 (28.43)	44.39 (29.44)
SE	3.94	6.58
Median	40.69	36.63
Min, Max	3.5, 95.8	8.0, 130.0
Change from baseline		
n	52	20
Mean (SD)	0.17 (6.17)	-3.37 (11.77)
SE	0.86	2.63
Median	0.00	-0.25
Min, Max	-15.0, 16.0	-26.0, 18.0

NIS score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurological impairment (range = 0 to 244).

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Table 16.7
Neuropathy Impairment Score (NIS): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Genotype: V30M

Subgroup Visit	Vutrisiran (HELIOS-A) (N=54)	Patisiran (HELIOS-A) (N=20)
Month 18		
Actual Value		
n	52	19
Mean (SD)	45.96 (30.16)	46.42 (27.19)
SE	4.18	6.24
Median	46.13	38.00
Min, Max	3.0, 121.1	14.0, 120.5
Change from baseline		
n	52	19
Mean (SD)	3.08 (9.46)	0.44 (10.68)
SE	1.31	2.45
Median	2.25	2.13
Min, Max	-22.0, 22.1	-24.5, 23.0

NIS score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurological impairment (range = 0 to 244).

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Table 16.7
Neuropathy Impairment Score (NIS): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Genotype: non-V30M

Subgroup Visit	Vutrisiran (HELIOS-A) (N=68)	Patisiran (HELIOS-A) (N=22)
Baseline		
n	68	22
Mean (SD)	42.40 (29.21)	38.88 (27.38)
SE	3.54	5.84
Median	33.00	33.75
Min, Max	5.5, 127.0	5.5, 89.4
Month 9		
Actual Value		
n	65	20
Mean (SD)	41.06 (29.37)	37.02 (30.61)
SE	3.64	6.84
Median	30.00	28.25
Min, Max	3.0, 132.6	2.0, 100.3
Change from baseline		
n	65	20
Mean (SD)	-0.52 (9.29)	1.66 (13.38)
SE	1.15	2.99
Median	0.50	-2.00
Min, Max	-20.4, 33.0	-27.0, 43.9

NIS score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurological impairment (range = 0 to 244).

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

Alnylam Pharmaceuticals Inc.
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Table 16.7
Neuropathy Impairment Score (NIS): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Genotype: non-V30M

Subgroup Visit	Vutrisiran (HELIOS-A) (N=68)	Patisiran (HELIOS-A) (N=22)
Month 18		
Actual Value		
n	63	17
Mean (SD)	44.30 (34.02)	39.08 (39.15)
SE	4.29	9.49
Median	32.50	25.00
Min, Max	0.0, 151.3	3.5, 134.4
Change from baseline		
n	63	17
Mean (SD)	2.24 (13.59)	5.39 (23.53)
SE	1.71	5.71
Median	0.00	1.00
Min, Max	-21.0, 67.5	-38.5, 81.1

NIS score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurological impairment (range = 0 to 244).

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Table 16.7
Neuropathy Impairment Score (NIS): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

FAP Stage: I

Subgroup Visit	Vutrisiran (HELIOS-A) (N=84)	Patisiran (HELIOS-A) (N=31)
Baseline		
n	84	31
Mean (SD)	31.54 (22.07)	32.44 (22.30)
SE	2.41	4.01
Median	25.75	29.00
Min, Max	5.0, 105.4	5.5, 102.9
Month 9		
Actual Value		
n	82	30
Mean (SD)	30.49 (22.03)	30.80 (23.85)
SE	2.43	4.35
Median	25.25	27.25
Min, Max	3.0, 95.8	2.0, 97.1
Change from baseline		
n	82	30
Mean (SD)	-0.35 (7.59)	0.01 (12.38)
SE	0.84	2.26
Median	-0.25	0.25
Min, Max	-20.4, 33.0	-27.0, 43.9

NIS score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurological impairment (range = 0 to 244).

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Table 16.7
Neuropathy Impairment Score (NIS): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

FAP Stage: I

Subgroup Visit	Vutrisiran (HELIOS-A) (N=84)	Patisiran (HELIOS-A) (N=31)
Month 18		
Actual Value		
n	81	29
Mean (SD)	32.93 (25.05)	32.95 (26.43)
SE	2.78	4.91
Median	27.00	28.50
Min, Max	0.0, 106.9	3.5, 134.4
Change from baseline		
n	81	29
Mean (SD)	1.95 (11.87)	2.03 (19.12)
SE	1.32	3.55
Median	0.50	2.00
Min, Max	-21.0, 67.5	-38.5, 81.1

NIS score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurological impairment (range = 0 to 244).

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Table 16.7
Neuropathy Impairment Score (NIS): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

FAP Stage: II&III

Subgroup Visit	Vutrisiran (HELIOS-A) (N=38)	Patisiran (HELIOS-A) (N=11)
Baseline		
n	38	11
Mean (SD)	68.38 (25.08)	73.16 (20.72)
SE	4.07	6.25
Median	73.06	70.00
Min, Max	16.0, 127.0	37.5, 115.6
Month 9		
Actual Value		
n	35	10
Mean (SD)	68.77 (25.04)	70.40 (27.00)
SE	4.23	8.54
Median	70.88	65.25
Min, Max	18.0, 132.6	32.9, 130.0
Change from baseline		
n	35	10
Mean (SD)	0.10 (9.10)	-3.46 (13.94)
SE	1.54	4.41
Median	1.13	-4.19
Min, Max	-18.8, 16.0	-26.0, 16.5

NIS score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurological impairment (range = 0 to 244).

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Table 16.7
Neuropathy Impairment Score (NIS): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

FAP Stage: II&III

Subgroup Visit	Vutrisiran (HELIOS-A) (N=38)	Patisiran (HELIOS-A) (N=11)
Month 18		
Actual Value		
n	34	7
Mean (SD)	73.93 (29.01)	84.41 (25.23)
SE	4.97	9.54
Median	71.13	74.38
Min, Max	20.5, 151.3	59.3, 120.5
Change from baseline		
n	34	7
Mean (SD)	4.22 (11.86)	5.89 (11.63)
SE	2.03	4.40
Median	2.56	2.13
Min, Max	-22.0, 30.6	-3.8, 30.0

NIS score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurological impairment (range = 0 to 244).

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Table 16.7
Neuropathy Impairment Score (NIS): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Cardiac Subpopulation: Yes

Subgroup Visit	Vutrisiran (HELIOS-A) (N=40)	Patisiran (HELIOS-A) (N=14)
Baseline		
n	40	14
Mean (SD)	55.42 (27.58)	51.96 (30.75)
SE	4.36	8.22
Median	56.38	52.38
Min, Max	13.0, 127.0	8.0, 115.6
Month 9		
Actual Value		
n	38	14
Mean (SD)	54.41 (30.04)	59.86 (34.50)
SE	4.87	9.22
Median	52.25	61.25
Min, Max	3.0, 132.6	6.0, 130.0
Change from baseline		
n	38	14
Mean (SD)	-1.11 (7.40)	7.90 (13.29)
SE	1.20	3.55
Median	-0.75	6.75
Min, Max	-20.4, 11.0	-9.0, 43.9

NIS score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurological impairment (range = 0 to 244).

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Table 16.7
Neuropathy Impairment Score (NIS): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Cardiac Subpopulation: Yes

Subgroup Visit	Vutrisiran (HELIOS-A) (N=40)	Patisiran (HELIOS-A) (N=14)
Month 18		
Actual Value		
n	37	13
Mean (SD)	56.82 (32.19)	60.26 (42.31)
SE	5.29	11.73
Median	57.88	56.00
Min, Max	0.0, 151.3	9.0, 134.4
Change from baseline		
n	37	13
Mean (SD)	2.05 (14.96)	9.69 (26.64)
SE	2.46	7.39
Median	2.00	4.88
Min, Max	-22.0, 67.5	-38.5, 81.1

NIS score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurological impairment (range = 0 to 244).

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Table 16.7
Neuropathy Impairment Score (NIS): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Cardiac Subpopulation: No

Subgroup Visit	Vutrisiran (HELIOS-A) (N=82)	Patisiran (HELIOS-A) (N=28)
Baseline		
n	82	28
Mean (SD)	36.97 (27.30)	38.68 (26.34)
SE	3.02	4.98
Median	29.50	34.75
Min, Max	5.0, 116.9	5.5, 102.9
Month 9		
Actual Value		
n	79	26
Mean (SD)	35.94 (26.41)	30.39 (21.39)
SE	2.97	4.19
Median	29.00	27.25
Min, Max	3.5, 118.0	2.0, 87.5
Change from baseline		
n	79	26
Mean (SD)	0.22 (8.33)	-5.57 (9.67)
SE	0.94	1.90
Median	0.00	-3.50
Min, Max	-18.8, 33.0	-27.0, 6.6

NIS score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurological impairment (range = 0 to 244).

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Table 16.7
Neuropathy Impairment Score (NIS): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Cardiac Subpopulation: No

Subgroup Visit	Vutrisiran (HELIOS-A) (N=82)	Patisiran (HELIOS-A) (N=28)
Month 18		
Actual Value		
n	78	23
Mean (SD)	39.47 (30.86)	33.17 (22.09)
SE	3.49	4.61
Median	29.50	28.50
Min, Max	0.0, 124.0	3.5, 84.0
Change from baseline		
n	78	23
Mean (SD)	2.89 (10.16)	-1.13 (8.64)
SE	1.15	1.80
Median	0.75	1.11
Min, Max	-21.0, 30.6	-24.5, 12.5

NIS score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurological impairment (range = 0 to 244).

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Table 16.7
Neuropathy Impairment Score (NIS): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Weight (kg): <65

Subgroup Visit	Vutrisiran (HELIOS-A) (N=46)	Patisiran (HELIOS-A) (N=15)
Baseline		
n	46	15
Mean (SD)	51.55 (27.91)	41.40 (29.90)
SE	4.12	7.72
Median	50.88	38.75
Min, Max	12.0, 127.0	8.0, 115.6
Month 9		
Actual Value		
n	44	15
Mean (SD)	51.20 (30.23)	40.43 (35.48)
SE	4.56	9.16
Median	52.25	34.50
Min, Max	3.0, 132.6	2.0, 130.0
Change from baseline		
n	44	15
Mean (SD)	-0.27 (7.37)	-0.97 (15.83)
SE	1.11	4.09
Median	0.38	-2.00
Min, Max	-15.0, 16.0	-21.0, 43.9

NIS score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurological impairment (range = 0 to 244).

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Table 16.7
Neuropathy Impairment Score (NIS): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Weight (kg): <65

Subgroup Visit	Vutrisiran (HELIOS-A) (N=46)	Patisiran (HELIOS-A) (N=15)
Month 18		
Actual Value		
n	42	13
Mean (SD)	52.44 (32.99)	41.47 (41.78)
SE	5.09	11.59
Median	56.13	27.00
Min, Max	0.0, 151.3	3.5, 134.4
Change from baseline		
n	42	13
Mean (SD)	2.23 (11.79)	2.05 (27.53)
SE	1.82	7.64
Median	0.25	2.00
Min, Max	-22.0, 30.6	-38.5, 81.1

NIS score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurological impairment (range = 0 to 244).

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Table 16.7
Neuropathy Impairment Score (NIS): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Weight (kg): ≥65

Subgroup Visit	Vutrisiran (HELIOS-A) (N=76)	Patisiran (HELIOS-A) (N=27)
Baseline		
n	76	27
Mean (SD)	37.85 (27.99)	44.06 (27.80)
SE	3.21	5.35
Median	30.25	36.50
Min, Max	5.0, 116.9	5.5, 102.9
Month 9		
Actual Value		
n	73	25
Mean (SD)	36.36 (26.68)	40.87 (26.76)
SE	3.12	5.35
Median	28.50	32.88
Min, Max	3.5, 118.0	6.0, 100.3
Change from baseline		
n	73	25
Mean (SD)	-0.18 (8.45)	-0.79 (10.75)
SE	0.99	2.15
Median	0.00	0.50
Min, Max	-20.4, 33.0	-27.0, 18.0

NIS score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurological impairment (range = 0 to 244).

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Table 16.7
Neuropathy Impairment Score (NIS): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Weight (kg): ≥65

Subgroup Visit	Vutrisiran (HELIOS-A) (N=76)	Patisiran (HELIOS-A) (N=27)
Month 18		
Actual Value		
n	73	23
Mean (SD)	40.80 (31.18)	43.79 (28.06)
SE	3.65	5.85
Median	31.00	35.50
Min, Max	0.0, 124.0	9.0, 119.4
Change from baseline		
n	73	23
Mean (SD)	2.85 (11.97)	3.19 (9.58)
SE	1.40	2.00
Median	1.50	2.50
Min, Max	-21.0, 67.5	-18.9, 30.0

NIS score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurological impairment (range = 0 to 244).

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NIS-Gesamtwert (Binäre Analyse)

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Table 16.4
Neuropathy Impairment Score (NIS)
Binary Subgroup Analysis
mITT Population

Month 9

Analysis Visit Statistics	Vutrisiran (HELIOS-A) (N=122)	Patisiran (HELIOS-A) (N=42)
Age (years)		
<65		
Patients included in analysis, N1	76	31
<0 point increase from baseline, n(%)	36 (47.4)	17 (54.8)
≥0 point increase from baseline, n(%)	38 (50.0)	13 (41.9)
Missing, n(%)	2 (2.6)	1 (3.2)
<0 point increase from baseline, (95% CI)	47.4 (36.1, 58.6)	54.8 (37.3, 72.4)
Percentage difference (Vutrisiran − Patisiran), (95% CI)	-7.470 (-28.277, 13.336)	
Odds ratio (Vutrisiran/Patisiran), (95% CI) [1]	0.741 (0.320, 1.714)	
Relative risk (Vutrisiran/Patisiran), (95% CI) [1]	0.864 (0.580, 1.286)	
P-value [2]	0.4705	

NIS score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurological impairment (range = 0 to 244).
N1 = Patients with missing postbaseline values due to COVID-19 or after initiation of local standard treatment for hATTR amyloidosis were included in analysis.
[1] Based on unstratified analysis.
In estimation of the odds ratio and relative risk, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the percentage difference or p-value.
[2] p-value based on the Wald test testing whether the relative risk equals to 1.
[3] p-value from a logistic regression using the penalized likelihood estimation (the FIRTH option) and with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Table 16.4
Neuropathy Impairment Score (NIS)
Binary Subgroup Analysis
mITT Population

Month 9

Analysis Visit Statistics	Vutrisiran (HELIOS-A) (N=122)	Patisiran (HELIOS-A) (N=42)
≥65		
Patients included in analysis, N1	46	11
<0 point increase from baseline, n(%)	20 (43.5)	4 (36.4)
≥0 point increase from baseline, n(%)	23 (50.0)	6 (54.5)
Missing, n(%)	3 (6.5)	1 (9.1)
<0 point increase from baseline, (95% CI)	43.5 (29.2, 57.8)	36.4 (7.9, 64.8)
Percentage difference (Vutrisiran – Patisiran), (95% CI)	7.115 (-24.718, 38.948)	
Odds ratio (Vutrisiran/Patisiran), (95% CI) [1]	1.346 (0.346, 5.244)	
Relative risk (Vutrisiran/Patisiran), (95% CI) [1]	1.196 (0.512, 2.793)	
P-value [2]	0.6797	
p-value of Treatment*Age [3]	0.5010	

NIS score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurological impairment (range = 0 to 244).
N1 = Patients with missing postbaseline values due to COVID-19 or after initiation of local standard treatment for hATTR amyloidosis were included in analysis.
[1] Based on unstratified analysis.
In estimation of the odds ratio and relative risk, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the percentage difference or p-value.
[2] p-value based on the Wald test testing whether the relative risk equals to 1.
[3] p-value from a logistic regression using the penalized likelihood estimation (the FIRTH option) and with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Table 16.4
Neuropathy Impairment Score (NIS)
Binary Subgroup Analysis
mITT Population

Month 18

Analysis Visit Statistics	Vutrisiran (HELIOS-A) (N=122)	Patisiran (HELIOS-A) (N=42)
Age (years)		
<65		
Patients included in analysis, N1	76	31
<0 point increase from baseline, n(%)	31 (40.8)	8 (25.8)
≥0 point increase from baseline, n(%)	43 (56.6)	19 (61.3)
Missing, n(%)	2 (2.6)	4 (12.9)
<0 point increase from baseline, (95% CI)	40.8 (29.7, 51.8)	25.8 (10.4, 41.2)
Percentage difference (Vutrisiran – Patisiran), (95% CI)	14.983 (-3.973, 33.939)	
Odds ratio (Vutrisiran/Patisiran), (95% CI) [1]	1.981 (0.785, 4.997)	
Relative risk (Vutrisiran/Patisiran), (95% CI) [1]	1.581 (0.821, 3.044)	
P-value [2]	0.1710	

NIS score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurological impairment (range = 0 to 244).
N1 = Patients with missing postbaseline values due to COVID-19 or after initiation of local standard treatment for hATTR amyloidosis were included in analysis.
[1] Based on unstratified analysis.
In estimation of the odds ratio and relative risk, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the percentage difference or p-value.
[2] p-value based on the Wald test testing whether the relative risk equals to 1.
[3] p-value from a logistic regression using the penalized likelihood estimation (the FIRTH option) and with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Table 16.4
Neuropathy Impairment Score (NIS)
Binary Subgroup Analysis
mITT Population

Month 18

Analysis Visit Statistics	Vutrisiran (HELIOS-A) (N=122)	Patisiran (HELIOS-A) (N=42)
≥65		
Patients included in analysis, N1	46	11
<0 point increase from baseline, n(%)	18 (39.1)	3 (27.3)
≥0 point increase from baseline, n(%)	23 (50.0)	6 (54.5)
Missing, n(%)	5 (10.9)	2 (18.2)
<0 point increase from baseline, (95% CI)	39.1 (25.0, 53.2)	27.3 (1.0, 53.6)
Percentage difference (Vutrisiran – Patisiran), (95% CI)	11.858 (-18.002, 41.717)	
Odds ratio (Vutrisiran/Patisiran), (95% CI) [1]	1.714 (0.401, 7.330)	
Relative risk (Vutrisiran/Patisiran), (95% CI) [1]	1.435 (0.512, 4.019)	
P-value [2]	0.4922	
p-value of Treatment*Age [3]	0.8229	

NIS score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurological impairment (range = 0 to 244).
N1 = Patients with missing postbaseline values due to COVID-19 or after initiation of local standard treatment for hATTR amyloidosis were included in analysis.
[1] Based on unstratified analysis.
In estimation of the odds ratio and relative risk, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the percentage difference or p-value.
[2] p-value based on the Wald test testing whether the relative risk equals to 1.
[3] p-value from a logistic regression using the penalized likelihood estimation (the FIRTH option) and with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Table 16.4
Neuropathy Impairment Score (NIS)
Binary Subgroup Analysis
mITT Population

Month 9

Analysis Visit Statistics	Vutrisiran (HELIOS-A) (N=122)	Patisiran (HELIOS-A) (N=42)
Sex		
Male		
Patients included in analysis, N1	79	27
<0 point increase from baseline, n(%)	37 (46.8)	13 (48.1)
≥0 point increase from baseline, n(%)	39 (49.4)	12 (44.4)
Missing, n(%)	3 (3.8)	2 (7.4)
<0 point increase from baseline, (95% CI)	46.8 (35.8, 57.8)	48.1 (29.3, 67.0)
Percentage difference (Vutrisiran – Patisiran), (95% CI)	-1.313 (-23.137, 20.511)	
Odds ratio (Vutrisiran/Patisiran), (95% CI) [1]	0.949 (0.396, 2.275)	
Relative risk (Vutrisiran/Patisiran), (95% CI) [1]	0.973 (0.616, 1.536)	
P-value [2]	0.9055	

NIS score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurological impairment (range = 0 to 244).
N1 = Patients with missing postbaseline values due to COVID-19 or after initiation of local standard treatment for hATTR amyloidosis were included in analysis.
[1] Based on unstratified analysis.
In estimation of the odds ratio and relative risk, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the percentage difference or p-value.
[2] p-value based on the Wald test testing whether the relative risk equals to 1.
[3] p-value from a logistic regression using the penalized likelihood estimation (the FIRTH option) and with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Alnylam Pharmaceuticals Inc.
ALN-TTRSC02-002

Table 16.4
Neuropathy Impairment Score (NIS)
Binary Subgroup Analysis
mITT Population

Month 9

Analysis Visit Statistics	Vutrisiran (HELIOS-A) (N=122)	Patisiran (HELIOS-A) (N=42)
Female		
Patients included in analysis, N1	43	15
<0 point increase from baseline, n(%)	19 (44.2)	8 (53.3)
≥0 point increase from baseline, n(%)	22 (51.2)	7 (46.7)
Missing, n(%)	2 (4.7)	0
<0 point increase from baseline, (95% CI)	44.2 (29.3, 59.0)	53.3 (28.1, 78.6)
Percentage difference (Vutrisiran – Patisiran), (95% CI)	-9.147 (-38.434, 20.140)	
Odds ratio (Vutrisiran/Patisiran), (95% CI) [1]	0.693 (0.213, 2.253)	
Relative risk (Vutrisiran/Patisiran), (95% CI) [1]	0.828 (0.464, 1.480)	
P-value [2]	0.5252	
p-value of Treatment*Sex [3]	0.6890	

NIS score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurological impairment (range = 0 to 244).
N1 = Patients with missing postbaseline values due to COVID-19 or after initiation of local standard treatment for hATTR amyloidosis were included in analysis.
[1] Based on unstratified analysis.
In estimation of the odds ratio and relative risk, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the percentage difference or p-value.
[2] p-value based on the Wald test testing whether the relative risk equals to 1.
[3] p-value from a logistic regression using the penalized likelihood estimation (the FIRTH option) and with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Alnylam Pharmaceuticals Inc.
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Table 16.4
Neuropathy Impairment Score (NIS)
Binary Subgroup Analysis
mITT Population

Month 18

Analysis Visit Statistics	Vutrisiran (HELIOS-A) (N=122)	Patisiran (HELIOS-A) (N=42)
Sex		
Male		
Patients included in analysis, N1	79	27
<0 point increase from baseline, n(%)	32 (40.5)	7 (25.9)
≥0 point increase from baseline, n(%)	42 (53.2)	15 (55.6)
Missing, n(%)	5 (6.3)	5 (18.5)
<0 point increase from baseline, (95% CI)	40.5 (29.7, 51.3)	25.9 (9.4, 42.5)
Percentage difference (Vutrisiran – Patisiran), (95% CI)	14.580 (-5.179, 34.339)	
Odds ratio (Vutrisiran/Patisiran), (95% CI) [1]	1.945 (0.737, 5.136)	
Relative risk (Vutrisiran/Patisiran), (95% CI) [1]	1.562 (0.783, 3.119)	
P-value [2]	0.2058	

NIS score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurological impairment (range = 0 to 244).
N1 = Patients with missing postbaseline values due to COVID-19 or after initiation of local standard treatment for hATTR amyloidosis were included in analysis.
[1] Based on unstratified analysis.
In estimation of the odds ratio and relative risk, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the percentage difference or p-value.
[2] p-value based on the Wald test testing whether the relative risk equals to 1.
[3] p-value from a logistic regression using the penalized likelihood estimation (the FIRTH option) and with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Table 16.4
Neuropathy Impairment Score (NIS)
Binary Subgroup Analysis
mITT Population

Month 18

Analysis Visit Statistics	Vutrisiran (HELIOS-A) (N=122)	Patisiran (HELIOS-A) (N=42)
Female		
Patients included in analysis, N1	43	15
<0 point increase from baseline, n(%)	17 (39.5)	4 (26.7)
≥0 point increase from baseline, n(%)	24 (55.8)	10 (66.7)
Missing, n(%)	2 (4.7)	1 (6.7)
<0 point increase from baseline, (95% CI)	39.5 (24.9, 54.1)	26.7 (4.3, 49.0)
Percentage difference (Vutrisiran – Patisiran), (95% CI)	12.868 (-13.859, 39.596)	
Odds ratio (Vutrisiran/Patisiran), (95% CI) [1]	1.798 (0.491, 6.581)	
Relative risk (Vutrisiran/Patisiran), (95% CI) [1]	1.483 (0.593, 3.709)	
P-value [2]	0.4000	
p-value of Treatment*Sex [3]	0.9000	

NIS score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurological impairment (range = 0 to 244).
N1 = Patients with missing postbaseline values due to COVID-19 or after initiation of local standard treatment for hATTR amyloidosis were included in analysis.
[1] Based on unstratified analysis.
In estimation of the odds ratio and relative risk, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the percentage difference or p-value.
[2] p-value based on the Wald test testing whether the relative risk equals to 1.
[3] p-value from a logistic regression using the penalized likelihood estimation (the FIRTH option) and with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Table 16.4
Neuropathy Impairment Score (NIS)
Binary Subgroup Analysis
mITT Population

Month 9

Analysis Visit Statistics	Vutrisiran (HELIOS-A) (N=122)	Patisiran (HELIOS-A) (N=42)
Race		
White		
Patients included in analysis, N1	86	29
<0 point increase from baseline, n(%)	44 (51.2)	12 (41.4)
≥0 point increase from baseline, n(%)	39 (45.3)	16 (55.2)
Missing, n(%)	3 (3.5)	1 (3.4)
<0 point increase from baseline, (95% CI)	51.2 (40.6, 61.7)	41.4 (23.5, 59.3)
Percentage difference (Vutrisiran – Patisiran), (95% CI)	9.783 (-11.023, 30.590)	
Odds ratio (Vutrisiran/Patisiran), (95% CI) [1]	1.484 (0.633, 3.477)	
Relative risk (Vutrisiran/Patisiran), (95% CI) [1]	1.236 (0.765, 1.998)	
P-value [2]	0.3861	

NIS score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurological impairment (range = 0 to 244).
N1 = Patients with missing postbaseline values due to COVID-19 or after initiation of local standard treatment for hATTR amyloidosis were included in analysis.
[1] Based on unstratified analysis.
In estimation of the odds ratio and relative risk, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the percentage difference or p-value.
[2] p-value based on the Wald test testing whether the relative risk equals to 1.
[3] p-value from a logistic regression using the penalized likelihood estimation (the FIRTH option) and with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Table 16.4
Neuropathy Impairment Score (NIS)
Binary Subgroup Analysis
mITT Population

Month 9

Analysis Visit Statistics	Vutrisiran (HELIOS-A) (N=122)	Patisiran (HELIOS-A) (N=42)
All Other Races		
Patients included in analysis, N1	36	13
<0 point increase from baseline, n(%)	12 (33.3)	9 (69.2)
≥0 point increase from baseline, n(%)	22 (61.1)	3 (23.1)
Missing, n(%)	2 (5.6)	1 (7.7)
<0 point increase from baseline, (95% CI)	33.3 (17.9, 48.7)	69.2 (44.1, 94.3)
Percentage difference (Vutrisiran – Patisiran), (95% CI)	-35.897 (-65.335, -6.460)	
Odds ratio (Vutrisiran/Patisiran), (95% CI) [1]	0.222 (0.057, 0.871)	
Relative risk (Vutrisiran/Patisiran), (95% CI) [1]	0.481 (0.268, 0.866)	
P-value [2]	0.0147	
p-value of Treatment*Race [3]	0.0271	

NIS score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurological impairment (range = 0 to 244).
N1 = Patients with missing postbaseline values due to COVID-19 or after initiation of local standard treatment for hATTR amyloidosis were included in analysis.
[1] Based on unstratified analysis.
In estimation of the odds ratio and relative risk, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the percentage difference or p-value.
[2] p-value based on the Wald test testing whether the relative risk equals to 1.
[3] p-value from a logistic regression using the penalized likelihood estimation (the FIRTH option) and with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Table 16.4
Neuropathy Impairment Score (NIS)
Binary Subgroup Analysis
mITT Population

Month 18

Analysis Visit Statistics	Vutrisiran (HELIOS-A) (N=122)	Patisiran (HELIOS-A) (N=42)
Race		
White		
Patients included in analysis, N1	86	29
<0 point increase from baseline, n(%)	36 (41.9)	8 (27.6)
≥0 point increase from baseline, n(%)	46 (53.5)	17 (58.6)
Missing, n(%)	4 (4.7)	4 (13.8)
<0 point increase from baseline, (95% CI)	41.9 (31.4, 52.3)	27.6 (11.3, 43.9)
Percentage difference (Vutrisiran – Patisiran), (95% CI)	14.274 (-5.047, 33.596)	
Odds ratio (Vutrisiran/Patisiran), (95% CI) [1]	1.890 (0.753, 4.743)	
Relative risk (Vutrisiran/Patisiran), (95% CI) [1]	1.517 (0.800, 2.878)	
P-value [2]	0.2016	

NIS score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurological impairment (range = 0 to 244).
N1 = Patients with missing postbaseline values due to COVID-19 or after initiation of local standard treatment for hATTR amyloidosis were included in analysis.
[1] Based on unstratified analysis.
In estimation of the odds ratio and relative risk, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the percentage difference or p-value.
[2] p-value based on the Wald test testing whether the relative risk equals to 1.
[3] p-value from a logistic regression using the penalized likelihood estimation (the FIRTH option) and with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Table 16.4
Neuropathy Impairment Score (NIS)
Binary Subgroup Analysis
mITT Population

Month 18

Analysis Visit Statistics	Vutrisiran (HELIOS-A) (N=122)	Patisiran (HELIOS-A) (N=42)
All Other Races		
Patients included in analysis, N1	36	13
<0 point increase from baseline, n(%)	13 (36.1)	3 (23.1)
≥0 point increase from baseline, n(%)	20 (55.6)	8 (61.5)
Missing, n(%)	3 (8.3)	2 (15.4)
<0 point increase from baseline, (95% CI)	36.1 (20.4, 51.8)	23.1 (0.2, 46.0)
Percentage difference (Vutrisiran – Patisiran), (95% CI)	13.034 (-14.728, 40.796)	
Odds ratio (Vutrisiran/Patisiran), (95% CI) [1]	1.884 (0.438, 8.100)	
Relative risk (Vutrisiran/Patisiran), (95% CI) [1]	1.565 (0.530, 4.624)	
P-value [2]	0.4179	
p-value of Treatment*Race [3]	0.9455	

NIS score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurological impairment (range = 0 to 244).
N1 = Patients with missing postbaseline values due to COVID-19 or after initiation of local standard treatment for hATTR amyloidosis were included in analysis.
[1] Based on unstratified analysis.
In estimation of the odds ratio and relative risk, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the percentage difference or p-value.
[2] p-value based on the Wald test testing whether the relative risk equals to 1.
[3] p-value from a logistic regression using the penalized likelihood estimation (the FIRTH option) and with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Table 16.4
Neuropathy Impairment Score (NIS)
Binary Subgroup Analysis
mITT Population

Month 9

Analysis Visit Statistics	Vutrisiran (HELIOS-A) (N=122)	Patisiran (HELIOS-A) (N=42)
Region		
North America		
Patients included in analysis, N1	27	8
<0 point increase from baseline, n(%)	14 (51.9)	4 (50.0)
≥0 point increase from baseline, n(%)	11 (40.7)	4 (50.0)
Missing, n(%)	2 (7.4)	0
<0 point increase from baseline, (95% CI)	51.9 (33.0, 70.7)	50.0 (15.4, 84.6)
Percentage difference (Vutrisiran – Patisiran), (95% CI)	1.852 (-37.590, 41.294)	
Odds ratio (Vutrisiran/Patisiran), (95% CI) [1]	1.077 (0.222, 5.219)	
Relative risk (Vutrisiran/Patisiran), (95% CI) [1]	1.037 (0.474, 2.268)	
P-value [2]	0.9274	

NIS score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurological impairment (range = 0 to 244).
N1 = Patients with missing postbaseline values due to COVID-19 or after initiation of local standard treatment for hATTR amyloidosis were included in analysis.
[1] Based on unstratified analysis.
In estimation of the odds ratio and relative risk, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the percentage difference or p-value.
[2] p-value based on the Wald test testing whether the relative risk equals to 1.
[3] p-value from a logistic regression using the penalized likelihood estimation (the FIRTH option) and with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Table 16.4
Neuropathy Impairment Score (NIS)
Binary Subgroup Analysis
mITT Population

Month 9

Analysis Visit Statistics	Vutrisiran (HELIOS-A) (N=122)	Patisiran (HELIOS-A) (N=42)
Western Europe		
Patients included in analysis, N1	42	20
<0 point increase from baseline, n(%)	21 (50.0)	8 (40.0)
≥0 point increase from baseline, n(%)	19 (45.2)	10 (50.0)
Missing, n(%)	2 (4.8)	2 (10.0)
<0 point increase from baseline, (95% CI)	50.0 (34.9, 65.1)	40.0 (18.5, 61.5)
Percentage difference (Vutrisiran – Patisiran), (95% CI)	10.000 (-16.261, 36.261)	
Odds ratio (Vutrisiran/Patisiran), (95% CI) [1]	1.500 (0.509, 4.417)	
Relative risk (Vutrisiran/Patisiran), (95% CI) [1]	1.250 (0.675, 2.315)	
P-value [2]	0.4778	

NIS score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurological impairment (range = 0 to 244).
N1 = Patients with missing postbaseline values due to COVID-19 or after initiation of local standard treatment for hATTR amyloidosis were included in analysis.
[1] Based on unstratified analysis.
In estimation of the odds ratio and relative risk, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the percentage difference or p-value.
[2] p-value based on the Wald test testing whether the relative risk equals to 1.
[3] p-value from a logistic regression using the penalized likelihood estimation (the FIRTH option) and with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Table 16.4
Neuropathy Impairment Score (NIS)
Binary Subgroup Analysis
mITT Population

Month 9

Analysis Visit Statistics	Vutrisiran (HELIOS-A) (N=122)	Patisiran (HELIOS-A) (N=42)
Rest of World		
Patients included in analysis, N1	53	14
<0 point increase from baseline, n(%)	21 (39.6)	9 (64.3)
≥0 point increase from baseline, n(%)	31 (58.5)	5 (35.7)
Missing, n(%)	1 (1.9)	0
<0 point increase from baseline, (95% CI)	39.6 (26.5, 52.8)	64.3 (39.2, 89.4)
Percentage difference (Vutrisiran - Patisiran), (95% CI)	-24.663 (-53.007, 3.681)	
Odds ratio (Vutrisiran/Patisiran), (95% CI) [1]	0.365 (0.107, 1.240)	
Relative risk (Vutrisiran/Patisiran), (95% CI) [1]	0.616 (0.369, 1.029)	
P-value [2]	0.0643	
p-value of Treatment*Region [3]	0.2565	

NIS score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurological impairment (range = 0 to 244).
N1 = Patients with missing postbaseline values due to COVID-19 or after initiation of local standard treatment for hATTR amyloidosis were included in analysis.
[1] Based on unstratified analysis.
In estimation of the odds ratio and relative risk, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the percentage difference or p-value.
[2] p-value based on the Wald test testing whether the relative risk equals to 1.
[3] p-value from a logistic regression using the penalized likelihood estimation (the FIRTH option) and with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Table 16.4
Neuropathy Impairment Score (NIS)
Binary Subgroup Analysis
mITT Population

Month 18

Analysis Visit Statistics	Vutrisiran (HELIOS-A) (N=122)	Patisiran (HELIOS-A) (N=42)
Region		
North America		
Patients included in analysis, N1	27	8
<0 point increase from baseline, n(%)	13 (48.1)	3 (37.5)
≥0 point increase from baseline, n(%)	12 (44.4)	3 (37.5)
Missing, n(%)	2 (7.4)	2 (25.0)
<0 point increase from baseline, (95% CI)	48.1 (29.3, 67.0)	37.5 (4.0, 71.0)
Percentage difference (Vutrisiran – Patisiran), (95% CI)	10.648 (-27.831, 49.127)	
Odds ratio (Vutrisiran/Patisiran), (95% CI) [1]	1.548 (0.307, 7.806)	
Relative risk (Vutrisiran/Patisiran), (95% CI) [1]	1.284 (0.484, 3.409)	
P-value [2]	0.6159	

NIS score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurological impairment (range = 0 to 244).
N1 = Patients with missing postbaseline values due to COVID-19 or after initiation of local standard treatment for hATTR amyloidosis were included in analysis.
[1] Based on unstratified analysis.
In estimation of the odds ratio and relative risk, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the percentage difference or p-value.
[2] p-value based on the Wald test testing whether the relative risk equals to 1.
[3] p-value from a logistic regression using the penalized likelihood estimation (the FIRTH option) and with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Table 16.4
Neuropathy Impairment Score (NIS)
Binary Subgroup Analysis
mITT Population

Month 18

Analysis Visit Statistics	Vutrisiran (HELIOS-A) (N=122)	Patisiran (HELIOS-A) (N=42)
Western Europe		
Patients included in analysis, N1	42	20
<0 point increase from baseline, n(%)	11 (26.2)	4 (20.0)
≥0 point increase from baseline, n(%)	29 (69.0)	13 (65.0)
Missing, n(%)	2 (4.8)	3 (15.0)
<0 point increase from baseline, (95% CI)	26.2 (12.9, 39.5)	20.0 (2.5, 37.5)
Percentage difference (Vutrisiran – Patisiran), (95% CI)	6.190 (-15.812, 28.193)	
Odds ratio (Vutrisiran/Patisiran), (95% CI) [1]	1.419 (0.389, 5.175)	
Relative risk (Vutrisiran/Patisiran), (95% CI) [1]	1.310 (0.476, 3.606)	
P-value [2]	0.6018	

NIS score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurological impairment (range = 0 to 244).
N1 = Patients with missing postbaseline values due to COVID-19 or after initiation of local standard treatment for hATTR amyloidosis were included in analysis.
[1] Based on unstratified analysis.
In estimation of the odds ratio and relative risk, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the percentage difference or p-value.
[2] p-value based on the Wald test testing whether the relative risk equals to 1.
[3] p-value from a logistic regression using the penalized likelihood estimation (the FIRTH option) and with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Table 16.4
Neuropathy Impairment Score (NIS)
Binary Subgroup Analysis
mITT Population

Month 18

Analysis Visit Statistics	Vutrisiran (HELIOS-A) (N=122)	Patisiran (HELIOS-A) (N=42)
Rest of World		
Patients included in analysis, N1	53	14
<0 point increase from baseline, n(%)	25 (47.2)	4 (28.6)
≥0 point increase from baseline, n(%)	25 (47.2)	9 (64.3)
Missing, n(%)	3 (5.7)	1 (7.1)
<0 point increase from baseline, (95% CI)	47.2 (33.7, 60.6)	28.6 (4.9, 52.2)
Percentage difference (Vutrisiran – Patisiran), (95% CI)	18.598 (-8.616, 45.812)	
Odds ratio (Vutrisiran/Patisiran), (95% CI) [1]	2.232 (0.621, 8.019)	
Relative risk (Vutrisiran/Patisiran), (95% CI) [1]	1.651 (0.688, 3.964)	
P-value [2]	0.2619	
p-value of Treatment*Region [3]	0.8793	

NIS score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurological impairment (range = 0 to 244).
N1 = Patients with missing postbaseline values due to COVID-19 or after initiation of local standard treatment for hATTR amyloidosis were included in analysis.
[1] Based on unstratified analysis.
In estimation of the odds ratio and relative risk, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the percentage difference or p-value.
[2] p-value based on the Wald test testing whether the relative risk equals to 1.
[3] p-value from a logistic regression using the penalized likelihood estimation (the FIRTH option) and with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Alnylam Pharmaceuticals Inc.
ALN-TTRSC02-002

Table 16.4
Neuropathy Impairment Score (NIS)
Binary Subgroup Analysis
mITT Population

Month 9

Analysis Visit Statistics	Vutrisiran (HELIOS-A) (N=122)	Patisiran (HELIOS-A) (N=42)
Baseline NIS		
<50		
Patients included in analysis, N1	78	27
<0 point increase from baseline, n(%)	38 (48.7)	13 (48.1)
≥0 point increase from baseline, n(%)	39 (50.0)	14 (51.9)
Missing, n(%)	1 (1.3)	0
<0 point increase from baseline, (95% CI)	48.7 (37.6, 59.8)	48.1 (29.3, 67.0)
Percentage difference (Vutrisiran – Patisiran), (95% CI)	0.570 (-21.299, 22.439)	
Odds ratio (Vutrisiran/Patisiran), (95% CI) [1]	1.023 (0.426, 2.456)	
Relative risk (Vutrisiran/Patisiran), (95% CI) [1]	1.012 (0.643, 1.591)	
P-value [2]	0.9594	

NIS score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurological impairment (range = 0 to 244).
N1 = Patients with missing postbaseline values due to COVID-19 or after initiation of local standard treatment for hATTR amyloidosis were included in analysis.
[1] Based on unstratified analysis.
In estimation of the odds ratio and relative risk, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the percentage difference or p-value.
[2] p-value based on the Wald test testing whether the relative risk equals to 1.
[3] p-value from a logistic regression using the penalized likelihood estimation (the FIRTH option) and with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Alnylam Pharmaceuticals Inc.
ALN-TTRSC02-002

Table 16.4
Neuropathy Impairment Score (NIS)
Binary Subgroup Analysis
mITT Population

Month 9

Analysis Visit Statistics	Vutrisiran (HELIOS-A) (N=122)	Patisiran (HELIOS-A) (N=42)
≥50		
Patients included in analysis, N1	44	15
<0 point increase from baseline, n(%)	18 (40.9)	8 (53.3)
≥0 point increase from baseline, n(%)	22 (50.0)	5 (33.3)
Missing, n(%)	4 (9.1)	2 (13.3)
<0 point increase from baseline, (95% CI)	40.9 (26.4, 55.4)	53.3 (28.1, 78.6)
Percentage difference (Vutrisiran – Patisiran), (95% CI)	-12.424 (-41.552, 16.704)	
Odds ratio (Vutrisiran/Patisiran), (95% CI) [1]	0.606 (0.186, 1.969)	
Relative risk (Vutrisiran/Patisiran), (95% CI) [1]	0.767 (0.424, 1.386)	
P-value [2]	0.3797	
p-value of Treatment*Baseline NIS [3]	0.4999	

NIS score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurological impairment (range = 0 to 244).
N1 = Patients with missing postbaseline values due to COVID-19 or after initiation of local standard treatment for hATTR amyloidosis were included in analysis.
[1] Based on unstratified analysis.
In estimation of the odds ratio and relative risk, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the percentage difference or p-value.
[2] p-value based on the Wald test testing whether the relative risk equals to 1.
[3] p-value from a logistic regression using the penalized likelihood estimation (the FIRTH option) and with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Table 16.4
Neuropathy Impairment Score (NIS)
Binary Subgroup Analysis
mITT Population

Month 18

Analysis Visit Statistics	Vutrisiran (HELIOS-A) (N=122)	Patisiran (HELIOS-A) (N=42)
Baseline NIS		
<50		
Patients included in analysis, N1	78	27
<0 point increase from baseline, n(%)	33 (42.3)	7 (25.9)
≥0 point increase from baseline, n(%)	42 (53.8)	18 (66.7)
Missing, n(%)	3 (3.8)	2 (7.4)
<0 point increase from baseline, (95% CI)	42.3 (31.3, 53.3)	25.9 (9.4, 42.5)
Percentage difference (Vutrisiran – Patisiran), (95% CI)	16.382 (-3.454, 36.217)	
Odds ratio (Vutrisiran/Patisiran), (95% CI) [1]	2.095 (0.794, 5.532)	
Relative risk (Vutrisiran/Patisiran), (95% CI) [1]	1.632 (0.820, 3.248)	
P-value [2]	0.1631	

NIS score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurological impairment (range = 0 to 244).
N1 = Patients with missing postbaseline values due to COVID-19 or after initiation of local standard treatment for hATTR amyloidosis were included in analysis.
[1] Based on unstratified analysis.
In estimation of the odds ratio and relative risk, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the percentage difference or p-value.
[2] p-value based on the Wald test testing whether the relative risk equals to 1.
[3] p-value from a logistic regression using the penalized likelihood estimation (the FIRTH option) and with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Table 16.4
Neuropathy Impairment Score (NIS)
Binary Subgroup Analysis
mITT Population

Month 18

Analysis Visit Statistics	Vutrisiran (HELIOS-A) (N=122)	Patisiran (HELIOS-A) (N=42)
≥50		
Patients included in analysis, N1	44	15
<0 point increase from baseline, n(%)	16 (36.4)	4 (26.7)
≥0 point increase from baseline, n(%)	24 (54.5)	7 (46.7)
Missing, n(%)	4 (9.1)	4 (26.7)
<0 point increase from baseline, (95% CI)	36.4 (22.1, 50.6)	26.7 (4.3, 49.0)
Percentage difference (Vutrisiran – Patisiran), (95% CI)	9.697 (-16.814, 36.208)	
Odds ratio (Vutrisiran/Patisiran), (95% CI) [1]	1.571 (0.429, 5.759)	
Relative risk (Vutrisiran/Patisiran), (95% CI) [1]	1.364 (0.540, 3.442)	
P-value [2]	0.5114	
p-value of Treatment*Baseline NIS [3]	0.7069	

NIS score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurological impairment (range = 0 to 244).
N1 = Patients with missing postbaseline values due to COVID-19 or after initiation of local standard treatment for hATTR amyloidosis were included in analysis.
[1] Based on unstratified analysis.
In estimation of the odds ratio and relative risk, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the percentage difference or p-value.
[2] p-value based on the Wald test testing whether the relative risk equals to 1.
[3] p-value from a logistic regression using the penalized likelihood estimation (the FIRTH option) and with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Table 16.4
Neuropathy Impairment Score (NIS)
Binary Subgroup Analysis
mITT Population

Month 9

Analysis Visit Statistics	Vutrisiran (HELIOS-A) (N=122)	Patisiran (HELIOS-A) (N=42)
Previous Tetramer Stabilizer Use		
Yes		
Patients included in analysis, N1	75	33
<0 point increase from baseline, n(%)	42 (56.0)	16 (48.5)
≥0 point increase from baseline, n(%)	32 (42.7)	16 (48.5)
Missing, n(%)	1 (1.3)	1 (3.0)
<0 point increase from baseline, (95% CI)	56.0 (44.8, 67.2)	48.5 (31.4, 65.5)
Percentage difference (Vutrisiran – Patisiran), (95% CI)	7.515 (-12.904, 27.935)	
Odds ratio (Vutrisiran/Patisiran), (95% CI) [1]	1.352 (0.595, 3.073)	
Relative risk (Vutrisiran/Patisiran), (95% CI) [1]	1.155 (0.770, 1.731)	
P-value [2]	0.4854	

NIS score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurological impairment (range = 0 to 244).
N1 = Patients with missing postbaseline values due to COVID-19 or after initiation of local standard treatment for hATTR amyloidosis were included in analysis.
[1] Based on unstratified analysis.
In estimation of the odds ratio and relative risk, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the percentage difference or p-value.
[2] p-value based on the Wald test testing whether the relative risk equals to 1.
[3] p-value from a logistic regression using the penalized likelihood estimation (the FIRTH option) and with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Table 16.4
Neuropathy Impairment Score (NIS)
Binary Subgroup Analysis
mITT Population

Month 9

Analysis Visit Statistics	Vutrisiran (HELIOS-A) (N=122)	Patisiran (HELIOS-A) (N=42)
No		
Patients included in analysis, N1	47	9
<0 point increase from baseline, n(%)	14 (29.8)	5 (55.6)
≥0 point increase from baseline, n(%)	29 (61.7)	3 (33.3)
Missing, n(%)	4 (8.5)	1 (11.1)
<0 point increase from baseline, (95% CI)	29.8 (16.7, 42.9)	55.6 (23.1, 88.0)
Percentage difference (Vutrisiran – Patisiran), (95% CI)	-25.768 (-60.766, 9.229)	
Odds ratio (Vutrisiran/Patisiran), (95% CI) [1]	0.339 (0.079, 1.455)	
Relative risk (Vutrisiran/Patisiran), (95% CI) [1]	0.536 (0.258, 1.114)	
P-value [2]	0.0946	
p-value of Treatment*Previous Tetramer Stabilizer Use [3]	0.1169	

NIS score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurological impairment (range = 0 to 244).
N1 = Patients with missing postbaseline values due to COVID-19 or after initiation of local standard treatment for hATTR amyloidosis were included in analysis.
[1] Based on unstratified analysis.
In estimation of the odds ratio and relative risk, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the percentage difference or p-value.
[2] p-value based on the Wald test testing whether the relative risk equals to 1.
[3] p-value from a logistic regression using the penalized likelihood estimation (the FIRTH option) and with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Table 16.4
Neuropathy Impairment Score (NIS)
Binary Subgroup Analysis
mITT Population

Month 18

Analysis Visit Statistics	Vutrisiran (HELIOS-A) (N=122)	Patisiran (HELIOS-A) (N=42)
Previous Tetramer Stabilizer Use		
Yes		
Patients included in analysis, N1	75	33
<0 point increase from baseline, n(%)	31 (41.3)	7 (21.2)
≥0 point increase from baseline, n(%)	40 (53.3)	22 (66.7)
Missing, n(%)	4 (5.3)	4 (12.1)
<0 point increase from baseline, (95% CI)	41.3 (30.2, 52.5)	21.2 (7.3, 35.2)
Percentage difference (Vutrisiran – Patisiran), (95% CI)	20.121 (2.268, 37.975)	
Odds ratio (Vutrisiran/Patisiran), (95% CI) [1]	2.617 (1.009, 6.785)	
Relative risk (Vutrisiran/Patisiran), (95% CI) [1]	1.949 (0.957, 3.966)	
P-value [2]	0.0658	

NIS score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurological impairment (range = 0 to 244).
N1 = Patients with missing postbaseline values due to COVID-19 or after initiation of local standard treatment for hATTR amyloidosis were included in analysis.
[1] Based on unstratified analysis.
In estimation of the odds ratio and relative risk, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the percentage difference or p-value.
[2] p-value based on the Wald test testing whether the relative risk equals to 1.
[3] p-value from a logistic regression using the penalized likelihood estimation (the FIRTH option) and with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Table 16.4
Neuropathy Impairment Score (NIS)
Binary Subgroup Analysis
mITT Population

Month 18

Analysis Visit Statistics	Vutrisiran (HELIOS-A) (N=122)	Patisiran (HELIOS-A) (N=42)
No		
Patients included in analysis, N1	47	9
<0 point increase from baseline, n(%)	18 (38.3)	4 (44.4)
≥0 point increase from baseline, n(%)	26 (55.3)	3 (33.3)
Missing, n(%)	3 (6.4)	2 (22.2)
<0 point increase from baseline, (95% CI)	38.3 (24.4, 52.2)	44.4 (12.0, 76.9)
Percentage difference (Vutrisiran – Patisiran), (95% CI)	-6.147 (-41.460, 29.167)	
Odds ratio (Vutrisiran/Patisiran), (95% CI) [1]	0.776 (0.184, 3.276)	
Relative risk (Vutrisiran/Patisiran), (95% CI) [1]	0.862 (0.381, 1.948)	
P-value [2]	0.7206	
p-value of Treatment*Previous Tetramer Stabilizer Use [3]	0.1777	

NIS score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurological impairment (range = 0 to 244).
N1 = Patients with missing postbaseline values due to COVID-19 or after initiation of local standard treatment for hATTR amyloidosis were included in analysis.
[1] Based on unstratified analysis.
In estimation of the odds ratio and relative risk, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the percentage difference or p-value.
[2] p-value based on the Wald test testing whether the relative risk equals to 1.
[3] p-value from a logistic regression using the penalized likelihood estimation (the FIRTH option) and with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Table 16.4
Neuropathy Impairment Score (NIS)
Binary Subgroup Analysis
mITT Population

Month 9

Analysis Visit Statistics	Vutrisiran (HELIOS-A) (N=122)	Patisiran (HELIOS-A) (N=42)
Genotype		
V30M		
Patients included in analysis, N1	54	20
<0 point increase from baseline, n(%)	25 (46.3)	10 (50.0)
≥0 point increase from baseline, n(%)	27 (50.0)	10 (50.0)
Missing, n(%)	2 (3.7)	0
<0 point increase from baseline, (95% CI)	46.3 (33.0, 59.6)	50.0 (28.1, 71.9)
Percentage difference (Vutrisiran – Patisiran), (95% CI)	-3.704 (-29.337, 21.929)	
Odds ratio (Vutrisiran/Patisiran), (95% CI) [1]	0.862 (0.309, 2.407)	
Relative risk (Vutrisiran/Patisiran), (95% CI) [1]	0.926 (0.548, 1.564)	
P-value [2]	0.7735	

NIS score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurological impairment (range = 0 to 244).
N1 = Patients with missing postbaseline values due to COVID-19 or after initiation of local standard treatment for hATTR amyloidosis were included in analysis.
[1] Based on unstratified analysis.
In estimation of the odds ratio and relative risk, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the percentage difference or p-value.
[2] p-value based on the Wald test testing whether the relative risk equals to 1.
[3] p-value from a logistic regression using the penalized likelihood estimation (the FIRTH option) and with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Table 16.4
Neuropathy Impairment Score (NIS)
Binary Subgroup Analysis
mITT Population

Month 9

Analysis Visit Statistics	Vutrisiran (HELIOS-A) (N=122)	Patisiran (HELIOS-A) (N=42)
non-V30M		
Patients included in analysis, N1	68	22
<0 point increase from baseline, n(%)	31 (45.6)	11 (50.0)
≥0 point increase from baseline, n(%)	34 (50.0)	9 (40.9)
Missing, n(%)	3 (4.4)	2 (9.1)
<0 point increase from baseline, (95% CI)	45.6 (33.8, 57.4)	50.0 (29.1, 70.9)
Percentage difference (Vutrisiran – Patisiran), (95% CI)	-4.412 (-28.426, 19.602)	
Odds ratio (Vutrisiran/Patisiran), (95% CI) [1]	0.838 (0.320, 2.193)	
Relative risk (Vutrisiran/Patisiran), (95% CI) [1]	0.912 (0.557, 1.491)	
P-value [2]	0.7129	
p-value of Treatment*Genotype [3]	0.9681	

NIS score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurological impairment (range = 0 to 244).
N1 = Patients with missing postbaseline values due to COVID-19 or after initiation of local standard treatment for hATTR amyloidosis were included in analysis.
[1] Based on unstratified analysis.
In estimation of the odds ratio and relative risk, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the percentage difference or p-value.
[2] p-value based on the Wald test testing whether the relative risk equals to 1.
[3] p-value from a logistic regression using the penalized likelihood estimation (the FIRTH option) and with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Table 16.4
Neuropathy Impairment Score (NIS)
Binary Subgroup Analysis
mITT Population

Month 18

Analysis Visit Statistics	Vutrisiran (HELIOS-A) (N=122)	Patisiran (HELIOS-A) (N=42)
Genotype		
V30M		
Patients included in analysis, N1	54	20
<0 point increase from baseline, n(%)	18 (33.3)	5 (25.0)
≥0 point increase from baseline, n(%)	34 (63.0)	14 (70.0)
Missing, n(%)	2 (3.7)	1 (5.0)
<0 point increase from baseline, (95% CI)	33.3 (20.8, 45.9)	25.0 (6.0, 44.0)
Percentage difference (Vutrisiran – Patisiran), (95% CI)	8.333 (-14.431, 31.098)	
Odds ratio (Vutrisiran/Patisiran), (95% CI) [1]	1.500 (0.470, 4.783)	
Relative risk (Vutrisiran/Patisiran), (95% CI) [1]	1.333 (0.571, 3.112)	
P-value [2]	0.5059	

NIS score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurological impairment (range = 0 to 244).
N1 = Patients with missing postbaseline values due to COVID-19 or after initiation of local standard treatment for hATTR amyloidosis were included in analysis.
[1] Based on unstratified analysis.
In estimation of the odds ratio and relative risk, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the percentage difference or p-value.
[2] p-value based on the Wald test testing whether the relative risk equals to 1.
[3] p-value from a logistic regression using the penalized likelihood estimation (the FIRTH option) and with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Table 16.4
Neuropathy Impairment Score (NIS)
Binary Subgroup Analysis
mITT Population

Month 18

Analysis Visit Statistics	Vutrisiran (HELIOS-A) (N=122)	Patisiran (HELIOS-A) (N=42)
non-V30M		
Patients included in analysis, N1	68	22
<0 point increase from baseline, n(%)	31 (45.6)	6 (27.3)
≥0 point increase from baseline, n(%)	32 (47.1)	11 (50.0)
Missing, n(%)	5 (7.4)	5 (22.7)
<0 point increase from baseline, (95% CI)	45.6 (33.8, 57.4)	27.3 (8.7, 45.9)
Percentage difference (Vutrisiran – Patisiran), (95% CI)	18.316 (-3.741, 40.372)	
Odds ratio (Vutrisiran/Patisiran), (95% CI) [1]	2.234 (0.780, 6.402)	
Relative risk (Vutrisiran/Patisiran), (95% CI) [1]	1.672 (0.805, 3.469)	
P-value [2]	0.1678	
p-value of Treatment*Genotype [3]	0.6123	

NIS score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurological impairment (range = 0 to 244).
N1 = Patients with missing postbaseline values due to COVID-19 or after initiation of local standard treatment for hATTR amyloidosis were included in analysis.
[1] Based on unstratified analysis.
In estimation of the odds ratio and relative risk, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the percentage difference or p-value.
[2] p-value based on the Wald test testing whether the relative risk equals to 1.
[3] p-value from a logistic regression using the penalized likelihood estimation (the FIRTH option) and with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Table 16.4
Neuropathy Impairment Score (NIS)
Binary Subgroup Analysis
mITT Population

Month 9

Analysis Visit Statistics	Vutrisiran (HELIOS-A) (N=122)	Patisiran (HELIOS-A) (N=42)
FAP Stage		
I		
Patients included in analysis, N1	84	31
<0 point increase from baseline, n(%)	41 (48.8)	14 (45.2)
≥0 point increase from baseline, n(%)	41 (48.8)	16 (51.6)
Missing, n(%)	2 (2.4)	1 (3.2)
<0 point increase from baseline, (95% CI)	48.8 (38.1, 59.5)	45.2 (27.6, 62.7)
Percentage difference (Vutrisiran – Patisiran), (95% CI)	3.648 (-16.874, 24.170)	
Odds ratio (Vutrisiran/Patisiran), (95% CI) [1]	1.158 (0.507, 2.646)	
Relative risk (Vutrisiran/Patisiran), (95% CI) [1]	1.081 (0.692, 1.687)	
P-value [2]	0.7325	

NIS score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurological impairment (range = 0 to 244).
N1 = Patients with missing postbaseline values due to COVID-19 or after initiation of local standard treatment for hATTR amyloidosis were included in analysis.
[1] Based on unstratified analysis.
In estimation of the odds ratio and relative risk, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the percentage difference or p-value.
[2] p-value based on the Wald test testing whether the relative risk equals to 1.
[3] p-value from a logistic regression using the penalized likelihood estimation (the FIRTH option) and with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Table 16.4
Neuropathy Impairment Score (NIS)
Binary Subgroup Analysis
mITT Population

Month 9

Analysis Visit Statistics	Vutrisiran (HELIOS-A) (N=122)	Patisiran (HELIOS-A) (N=42)
II&III		
Patients included in analysis, N1	38	11
<0 point increase from baseline, n(%)	15 (39.5)	7 (63.6)
≥0 point increase from baseline, n(%)	20 (52.6)	3 (27.3)
Missing, n(%)	3 (7.9)	1 (9.1)
<0 point increase from baseline, (95% CI)	39.5 (23.9, 55.0)	63.6 (35.2, 92.1)
Percentage difference (Vutrisiran – Patisiran), (95% CI)	-24.163 (-56.561, 8.236)	
Odds ratio (Vutrisiran/Patisiran), (95% CI) [1]	0.373 (0.093, 1.496)	
Relative risk (Vutrisiran/Patisiran), (95% CI) [1]	0.620 (0.342, 1.125)	
P-value [2]	0.1160	
p-value of Treatment*FAP Stage [3]	0.1937	

NIS score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurological impairment (range = 0 to 244).
N1 = Patients with missing postbaseline values due to COVID-19 or after initiation of local standard treatment for hATTR amyloidosis were included in analysis.
[1] Based on unstratified analysis.
In estimation of the odds ratio and relative risk, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the percentage difference or p-value.
[2] p-value based on the Wald test testing whether the relative risk equals to 1.
[3] p-value from a logistic regression using the penalized likelihood estimation (the FIRTH option) and with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Alnylam Pharmaceuticals Inc.
ALN-TTRSC02-002

Table 16.4
Neuropathy Impairment Score (NIS)
Binary Subgroup Analysis
mITT Population

Month 18

Analysis Visit Statistics	Vutrisiran (HELIOS-A) (N=122)	Patisiran (HELIOS-A) (N=42)
FAP Stage		
I		
Patients included in analysis, N1	84	31
<0 point increase from baseline, n(%)	35 (41.7)	9 (29.0)
≥0 point increase from baseline, n(%)	46 (54.8)	20 (64.5)
Missing, n(%)	3 (3.6)	2 (6.5)
<0 point increase from baseline, (95% CI)	41.7 (31.1, 52.2)	29.0 (13.1, 45.0)
Percentage difference (Vutrisiran – Patisiran), (95% CI)	12.634 (-6.509, 31.778)	
Odds ratio (Vutrisiran/Patisiran), (95% CI) [1]	1.746 (0.718, 4.246)	
Relative risk (Vutrisiran/Patisiran), (95% CI) [1]	1.435 (0.783, 2.630)	
P-value [2]	0.2424	

NIS score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurological impairment (range = 0 to 244).
N1 = Patients with missing postbaseline values due to COVID-19 or after initiation of local standard treatment for hATTR amyloidosis were included in analysis.
[1] Based on unstratified analysis.
In estimation of the odds ratio and relative risk, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the percentage difference or p-value.
[2] p-value based on the Wald test testing whether the relative risk equals to 1.
[3] p-value from a logistic regression using the penalized likelihood estimation (the FIRTH option) and with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Alnylam Pharmaceuticals Inc.
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Table 16.4
Neuropathy Impairment Score (NIS)
Binary Subgroup Analysis
mITT Population

Month 18

Analysis Visit Statistics	Vutrisiran (HELIOS-A) (N=122)	Patisiran (HELIOS-A) (N=42)
II&III		
Patients included in analysis, N1	38	11
<0 point increase from baseline, n(%)	14 (36.8)	2 (18.2)
≥0 point increase from baseline, n(%)	20 (52.6)	5 (45.5)
Missing, n(%)	4 (10.5)	4 (36.4)
<0 point increase from baseline, (95% CI)	36.8 (21.5, 52.2)	18.2 (0.0, 41.0)
Percentage difference (Vutrisiran – Patisiran), (95% CI)	18.660 (-8.812, 46.133)	
Odds ratio (Vutrisiran/Patisiran), (95% CI) [1]	2.625 (0.495, 13.916)	
Relative risk (Vutrisiran/Patisiran), (95% CI) [1]	2.026 (0.541, 7.592)	
P-value [2]	0.2947	
p-value of Treatment*FAP Stage [3]	0.7634	

NIS score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurological impairment (range = 0 to 244).
N1 = Patients with missing postbaseline values due to COVID-19 or after initiation of local standard treatment for hATTR amyloidosis were included in analysis.
[1] Based on unstratified analysis.
In estimation of the odds ratio and relative risk, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the percentage difference or p-value.
[2] p-value based on the Wald test testing whether the relative risk equals to 1.
[3] p-value from a logistic regression using the penalized likelihood estimation (the FIRTH option) and with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Alnylam Pharmaceuticals Inc.
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Table 16.4
Neuropathy Impairment Score (NIS)
Binary Subgroup Analysis
mITT Population

Month 9

Analysis Visit Statistics	Vutrisiran (HELIOS-A) (N=122)	Patisiran (HELIOS-A) (N=42)
Cardiac Subpopulation		
Yes		
Patients included in analysis, N1	40	14
<0 point increase from baseline, n(%)	20 (50.0)	5 (35.7)
≥0 point increase from baseline, n(%)	18 (45.0)	9 (64.3)
Missing, n(%)	2 (5.0)	0
<0 point increase from baseline, (95% CI)	50.0 (34.5, 65.5)	35.7 (10.6, 60.8)
Percentage difference (Vutrisiran – Patisiran), (95% CI)	14.286 (-15.211, 43.783)	
Odds ratio (Vutrisiran/Patisiran), (95% CI) [1]	1.800 (0.512, 6.325)	
Relative risk (Vutrisiran/Patisiran), (95% CI) [1]	1.400 (0.649, 3.018)	
P-value [2]	0.3906	

NIS score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurological impairment (range = 0 to 244).
N1 = Patients with missing postbaseline values due to COVID-19 or after initiation of local standard treatment for hATTR amyloidosis were included in analysis.
[1] Based on unstratified analysis.
In estimation of the odds ratio and relative risk, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the percentage difference or p-value.
[2] p-value based on the Wald test testing whether the relative risk equals to 1.
[3] p-value from a logistic regression using the penalized likelihood estimation (the FIRTH option) and with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Alnylam Pharmaceuticals Inc.
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Table 16.4
Neuropathy Impairment Score (NIS)
Binary Subgroup Analysis
mITT Population

Month 9

Analysis Visit Statistics	Vutrisiran (HELIOS-A) (N=122)	Patisiran (HELIOS-A) (N=42)
No		
Patients included in analysis, N1	82	28
<0 point increase from baseline, n(%)	36 (43.9)	16 (57.1)
≥0 point increase from baseline, n(%)	43 (52.4)	10 (35.7)
Missing, n(%)	3 (3.7)	2 (7.1)
<0 point increase from baseline, (95% CI)	43.9 (33.2, 54.6)	57.1 (38.8, 75.5)
Percentage difference (Vutrisiran – Patisiran), (95% CI)	-13.240 (-34.486, 8.005)	
Odds ratio (Vutrisiran/Patisiran), (95% CI) [1]	0.587 (0.247, 1.396)	
Relative risk (Vutrisiran/Patisiran), (95% CI) [1]	0.768 (0.513, 1.150)	
P-value [2]	0.2003	
p-value of Treatment*Cardiac Subpopulation [3]	0.1696	

NIS score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurological impairment (range = 0 to 244).
N1 = Patients with missing postbaseline values due to COVID-19 or after initiation of local standard treatment for hATTR amyloidosis were included in analysis.
[1] Based on unstratified analysis.
In estimation of the odds ratio and relative risk, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the percentage difference or p-value.
[2] p-value based on the Wald test testing whether the relative risk equals to 1.
[3] p-value from a logistic regression using the penalized likelihood estimation (the FIRTH option) and with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Alnylam Pharmaceuticals Inc.
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Table 16.4
Neuropathy Impairment Score (NIS)
Binary Subgroup Analysis
mITT Population

Month 18

Analysis Visit Statistics	Vutrisiran (HELIOS-A) (N=122)	Patisiran (HELIOS-A) (N=42)
Cardiac Subpopulation		
Yes		
Patients included in analysis, N1	40	14
<0 point increase from baseline, n(%)	17 (42.5)	2 (14.3)
≥0 point increase from baseline, n(%)	20 (50.0)	11 (78.6)
Missing, n(%)	3 (7.5)	1 (7.1)
<0 point increase from baseline, (95% CI)	42.5 (27.2, 57.8)	14.3 (0.0, 32.6)
Percentage difference (Vutrisiran – Patisiran), (95% CI)	28.214 (4.325, 52.103)	
Odds ratio (Vutrisiran/Patisiran), (95% CI) [1]	4.435 (0.875, 22.475)	
Relative risk (Vutrisiran/Patisiran), (95% CI) [1]	2.975 (0.785, 11.280)	
P-value [2]	0.1089	

NIS score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurological impairment (range = 0 to 244).
N1 = Patients with missing postbaseline values due to COVID-19 or after initiation of local standard treatment for hATTR amyloidosis were included in analysis.
[1] Based on unstratified analysis.
In estimation of the odds ratio and relative risk, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the percentage difference or p-value.
[2] p-value based on the Wald test testing whether the relative risk equals to 1.
[3] p-value from a logistic regression using the penalized likelihood estimation (the FIRTH option) and with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Alnylam Pharmaceuticals Inc.
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Table 16.4
Neuropathy Impairment Score (NIS)
Binary Subgroup Analysis
mITT Population

Month 18

Analysis Visit Statistics	Vutrisiran (HELIOS-A) (N=122)	Patisiran (HELIOS-A) (N=42)
No		
Patients included in analysis, N1	82	28
<0 point increase from baseline, n(%)	32 (39.0)	9 (32.1)
≥0 point increase from baseline, n(%)	46 (56.1)	14 (50.0)
Missing, n(%)	4 (4.9)	5 (17.9)
<0 point increase from baseline, (95% CI)	39.0 (28.5, 49.6)	32.1 (14.8, 49.4)
Percentage difference (Vutrisiran – Patisiran), (95% CI)	6.882 (-13.385, 27.148)	
Odds ratio (Vutrisiran/Patisiran), (95% CI) [1]	1.351 (0.545, 3.353)	
Relative risk (Vutrisiran/Patisiran), (95% CI) [1]	1.214 (0.665, 2.217)	
P-value [2]	0.5279	
p-value of Treatment*Cardiac Subpopulation [3]	0.2554	

NIS score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurological impairment (range = 0 to 244).
N1 = Patients with missing postbaseline values due to COVID-19 or after initiation of local standard treatment for hATTR amyloidosis were included in analysis.
[1] Based on unstratified analysis.
In estimation of the odds ratio and relative risk, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the percentage difference or p-value.
[2] p-value based on the Wald test testing whether the relative risk equals to 1.
[3] p-value from a logistic regression using the penalized likelihood estimation (the FIRTH option) and with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Alnylam Pharmaceuticals Inc.
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Table 16.4
Neuropathy Impairment Score (NIS)
Binary Subgroup Analysis
mITT Population

Month 9

Analysis Visit Statistics	Vutrisiran (HELIOS-A) (N=122)	Patisiran (HELIOS-A) (N=42)
Weight (kg)		
<65 kg		
Patients included in analysis, N1	46	15
<0 point increase from baseline, n(%)	21 (45.7)	9 (60.0)
≥0 point increase from baseline, n(%)	23 (50.0)	6 (40.0)
Missing, n(%)	2 (4.3)	0
<0 point increase from baseline, (95% CI)	45.7 (31.3, 60.0)	60.0 (35.2, 84.8)
Percentage difference (Vutrisiran – Patisiran), (95% CI)	-14.348 (-43.015, 14.320)	
Odds ratio (Vutrisiran/Patisiran), (95% CI) [1]	0.560 (0.171, 1.831)	
Relative risk (Vutrisiran/Patisiran), (95% CI) [1]	0.761 (0.452, 1.279)	
P-value [2]	0.3027	

NIS score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurological impairment (range = 0 to 244).
N1 = Patients with missing postbaseline values due to COVID-19 or after initiation of local standard treatment for hATTR amyloidosis were included in analysis.
[1] Based on unstratified analysis.
In estimation of the odds ratio and relative risk, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the percentage difference or p-value.
[2] p-value based on the Wald test testing whether the relative risk equals to 1.
[3] p-value from a logistic regression using the penalized likelihood estimation (the FIRTH option) and with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Alnylam Pharmaceuticals Inc.
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Table 16.4
Neuropathy Impairment Score (NIS)
Binary Subgroup Analysis
mITT Population

Month 9

Analysis Visit Statistics	Vutrisiran (HELIOS-A) (N=122)	Patisiran (HELIOS-A) (N=42)
≥65 kg		
Patients included in analysis, N1	76	27
<0 point increase from baseline, n(%)	35 (46.1)	12 (44.4)
≥0 point increase from baseline, n(%)	38 (50.0)	13 (48.1)
Missing, n(%)	3 (3.9)	2 (7.4)
<0 point increase from baseline, (95% CI)	46.1 (34.8, 57.3)	44.4 (25.7, 63.2)
Percentage difference (Vutrisiran – Patisiran), (95% CI)	1.608 (-20.229, 23.446)	
Odds ratio (Vutrisiran/Patisiran), (95% CI) [1]	1.067 (0.441, 2.580)	
Relative risk (Vutrisiran/Patisiran), (95% CI) [1]	1.036 (0.637, 1.686)	
P-value [2]	0.8862	
p-value of Treatment*Weight (kg) [3]	0.4184	

NIS score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurological impairment (range = 0 to 244).
N1 = Patients with missing postbaseline values due to COVID-19 or after initiation of local standard treatment for hATTR amyloidosis were included in analysis.
[1] Based on unstratified analysis.
In estimation of the odds ratio and relative risk, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the percentage difference or p-value.
[2] p-value based on the Wald test testing whether the relative risk equals to 1.
[3] p-value from a logistic regression using the penalized likelihood estimation (the FIRTH option) and with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Alnylam Pharmaceuticals Inc.
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Table 16.4
Neuropathy Impairment Score (NIS)
Binary Subgroup Analysis
mITT Population

Month 18

Analysis Visit Statistics	Vutrisiran (HELIOS-A) (N=122)	Patisiran (HELIOS-A) (N=42)
Weight (kg)		
<65 kg		
Patients included in analysis, N1	46	15
<0 point increase from baseline, n(%)	19 (41.3)	5 (33.3)
≥0 point increase from baseline, n(%)	23 (50.0)	8 (53.3)
Missing, n(%)	4 (8.7)	2 (13.3)
<0 point increase from baseline, (95% CI)	41.3 (27.1, 55.5)	33.3 (9.5, 57.2)
Percentage difference (Vutrisiran – Patisiran), (95% CI)	7.971 (-19.806, 35.748)	
Odds ratio (Vutrisiran/Patisiran), (95% CI) [1]	1.407 (0.414, 4.784)	
Relative risk (Vutrisiran/Patisiran), (95% CI) [1]	1.239 (0.560, 2.742)	
P-value [2]	0.5967	

NIS score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurological impairment (range = 0 to 244).
N1 = Patients with missing postbaseline values due to COVID-19 or after initiation of local standard treatment for hATTR amyloidosis were included in analysis.
[1] Based on unstratified analysis.
In estimation of the odds ratio and relative risk, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the percentage difference or p-value.
[2] p-value based on the Wald test testing whether the relative risk equals to 1.
[3] p-value from a logistic regression using the penalized likelihood estimation (the FIRTH option) and with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Table 16.4
Neuropathy Impairment Score (NIS)
Binary Subgroup Analysis
mITT Population

Month 18

Analysis Visit Statistics	Vutrisiran (HELIOS-A) (N=122)	Patisiran (HELIOS-A) (N=42)
≥65 kg		
Patients included in analysis, N1	76	27
<0 point increase from baseline, n(%)	30 (39.5)	6 (22.2)
≥0 point increase from baseline, n(%)	43 (56.6)	17 (63.0)
Missing, n(%)	3 (3.9)	4 (14.8)
<0 point increase from baseline, (95% CI)	39.5 (28.5, 50.5)	22.2 (6.5, 37.9)
Percentage difference (Vutrisiran - Patisiran), (95% CI)	17.251 (-1.897, 36.400)	
Odds ratio (Vutrisiran/Patisiran), (95% CI) [1]	2.283 (0.825, 6.313)	
Relative risk (Vutrisiran/Patisiran), (95% CI) [1]	1.776 (0.832, 3.793)	
P-value [2]	0.1377	
p-value of Treatment*Weight (kg) [3]	0.5579	

NIS score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurological impairment (range = 0 to 244).
N1 = Patients with missing postbaseline values due to COVID-19 or after initiation of local standard treatment for hATTR amyloidosis were included in analysis.
[1] Based on unstratified analysis.
In estimation of the odds ratio and relative risk, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the percentage difference or p-value.
[2] p-value based on the Wald test testing whether the relative risk equals to 1.
[3] p-value from a logistic regression using the penalized likelihood estimation (the FIRTH option) and with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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NIS – Domäne NIS-*Weakness*

Siehe Domäne NIS-*Weakness* des mNIS+7

NIS – Domäne NIS-*Reflexes*

Siehe Domäne NIS-*Reflexes* des mNIS+7

NIS – Domäne NIS-*Sensation*

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Table 16.6
Neuropathy Impairment Score (NIS) Component Scores: Change from Baseline to Month 18, MMRM Model
Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A) Subgroup Analysis
mITT Population

Neuropathy Impairment Score - Sensation (NIS-S)

Subgroup Visit	LS Mean (95% CI) Vutrisiran (HELIOS-A) (N=122)	LS Mean (95% CI) Patisiran (HELIOS-A) (N=42)	LS Mean Difference (Vutrisiran-Patisiran) (95% CI), p-value	Standardized Effect Size (95% CI)
Age (years)				
<65	75	30		
Month 9	-0.18 (-0.96, 0.61)	-0.75 (-1.99, 0.49)	0.57 (-0.89, 2.04), 0.4412	0.16 (-0.26, 0.58)
Month 18	0.39 (-0.47, 1.26)	0.24 (-1.18, 1.65)	0.16 (-1.50, 1.82), 0.8524	0.04 (-0.39, 0.47)
≥65	44	10		
Month 9	0.24 (-0.77, 1.25)	-0.08 (-2.18, 2.01)	0.32 (-2.00, 2.64), 0.7852	0.10 (-0.58, 0.78)
Month 18	0.81 (-0.27, 1.89)	0.90 (-1.31, 3.11)	-0.10 (-2.55, 2.36), 0.9391	-0.02 (-0.73, 0.69)
p-value of Treatment*Age	0.8534			

NIS score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurological impairment (range = 0 to 244).
LS estimates and p-value derived from mixed-effects model for repeated measures (MMRM), controlling for categorical factors (treatment, visit), the subgroup variable, continuous covariate (baseline value), and interaction (treatment by visit, treatment by subgroup).
Standardized effect size (d) = LS mean difference/estimated pooled standard deviation with the small sample bias correction.

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Table 16.6
Neuropathy Impairment Score (NIS) Component Scores: Change from Baseline to Month 18, MMRM Model
Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A) Subgroup Analysis
mITT Population

Neuropathy Impairment Score - Sensation (NIS-S)

Subgroup Visit	LS Mean (95% CI) Vutrisiran (HELIOS-A) (N=122)	LS Mean (95% CI) Patisiran (HELIOS-A) (N=42)	LS Mean Difference (Vutrisiran-Patisiran) (95% CI), p-value	Standardized Effect Size (95% CI)
Sex				
Male	77	25		
Month 9	-0.05 (-0.82, 0.72)	-0.13 (-1.48, 1.21)	0.08 (-1.46, 1.63), 0.9143	0.02 (-0.42, 0.47)
Month 18	0.52 (-0.34, 1.38)	0.85 (-0.66, 2.37)	-0.33 (-2.08, 1.41), 0.7066	-0.08 (-0.55, 0.38)
Female	42	15		
Month 9	0.02 (-1.01, 1.05)	-1.33 (-3.04, 0.39)	1.35 (-0.65, 3.35), 0.1840	0.40 (-0.19, 0.99)
Month 18	0.59 (-0.51, 1.69)	-0.34 (-2.19, 1.51)	0.93 (-1.22, 3.08), 0.3932	0.23 (-0.37, 0.83)
p-value of Treatment*Sex	0.3127			

NIS score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurological impairment (range = 0 to 244).
LS estimates and p-value derived from mixed-effects model for repeated measures (MMRM), controlling for categorical factors (treatment, visit), the subgroup variable, continuous covariate (baseline value), and interaction (treatment by visit, treatment by subgroup).
Standardized effect size (d) = LS mean difference/estimated pooled standard deviation with the small sample bias correction.

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Table 16.6
Neuropathy Impairment Score (NIS) Component Scores: Change from Baseline to Month 18, MMRM Model
Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A) Subgroup Analysis
mITT Population

Neuropathy Impairment Score - Sensation (NIS-S)

Subgroup Visit	LS Mean (95% CI) Vutrisiran (HELIOS-A) (N=122)	LS Mean (95% CI) Patisiran (HELIOS-A) (N=42)	LS Mean Difference (Vutrisiran-Patisiran) (95% CI), p-value	Standardized Effect Size (95% CI)
Race				
White	84	28		
Month 9	0.04 (-0.70, 0.78)	-0.52 (-1.80, 0.77)	0.56 (-0.93, 2.04), 0.4601	0.15 (-0.27, 0.58)
Month 18	0.61 (-0.22, 1.44)	0.47 (-0.99, 1.93)	0.14 (-1.54, 1.82), 0.8699	0.03 (-0.40, 0.47)
All Other Races	35	12		
Month 9	-0.18 (-1.31, 0.95)	-0.74 (-2.68, 1.20)	0.56 (-1.68, 2.79), 0.6230	0.18 (-0.47, 0.83)
Month 18	0.39 (-0.80, 1.58)	0.25 (-1.81, 2.31)	0.14 (-2.23, 2.51), 0.9064	0.04 (-0.63, 0.71)
p-value of Treatment*Race	0.9987			

NIS score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurological impairment (range = 0 to 244).
LS estimates and p-value derived from mixed-effects model for repeated measures (MMRM), controlling for categorical factors (treatment, visit), the subgroup variable, continuous covariate (baseline value), and interaction (treatment by visit, treatment by subgroup).
Standardized effect size (d) = LS mean difference/estimated pooled standard deviation with the small sample bias correction.

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Table 16.6
Neuropathy Impairment Score (NIS) Component Scores: Change from Baseline to Month 18, MMRM Model
Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A) Subgroup Analysis
mITT Population

Neuropathy Impairment Score - Sensation (NIS-S)

Subgroup Visit	LS Mean (95% CI) Vutrisiran (HELIOS-A) (N=122)	LS Mean (95% CI) Patisiran (HELIOS-A) (N=42)	LS Mean Difference (Vutrisiran-Patisiran) (95% CI), p-value	Standardized Effect Size (95% CI)
Region				
North America	27	8		
Month 9	-0.47 (-1.83, 0.90)	-0.88 (-3.27, 1.50)	0.42 (-2.26, 3.10), 0.7594	0.13 (-0.65, 0.90)
Month 18	0.10 (-1.31, 1.52)	0.10 (-2.41, 2.61)	0.00 (-2.82, 2.82), 0.9994	0.00 (-0.87, 0.87)
Western Europe	40	18		
Month 9	0.29 (-0.77, 1.35)	-0.79 (-2.38, 0.80)	1.09 (-0.81, 2.98), 0.2596	0.31 (-0.24, 0.86)
Month 18	0.86 (-0.27, 1.99)	0.19 (-1.54, 1.92)	0.67 (-1.38, 2.72), 0.5201	0.20 (-0.35, 0.75)
Rest of World	52	14		
Month 9	-0.04 (-0.98, 0.89)	-0.14 (-1.93, 1.64)	0.10 (-1.92, 2.12), 0.9225	0.03 (-0.56, 0.61)
Month 18	0.53 (-0.49, 1.54)	0.84 (-1.08, 2.76)	-0.32 (-2.50, 1.87), 0.7754	-0.07 (-0.67, 0.53)
p-value of Treatment*Region	0.7665			

NIS score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurological impairment (range = 0 to 244).
LS estimates and p-value derived from mixed-effects model for repeated measures (MMRM), controlling for categorical factors (treatment, visit), the subgroup variable, continuous covariate (baseline value), and interaction (treatment by visit, treatment by subgroup).
Standardized effect size (d) = LS mean difference/estimated pooled standard deviation with the small sample bias correction.

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Table 16.6
Neuropathy Impairment Score (NIS) Component Scores: Change from Baseline to Month 18, MMRM Model
Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A) Subgroup Analysis
mITT Population

Neuropathy Impairment Score - Sensation (NIS-S)

Subgroup Visit	LS Mean (95% CI) Vutrisiran (HELIOS-A) (N=122)	LS Mean (95% CI) Patisiran (HELIOS-A) (N=42)	LS Mean Difference (Vutrisiran-Patisiran) (95% CI), p-value	Standardized Effect Size (95% CI)
Baseline NIS				
<50	77	27		
Month 9	-1.08 (-1.91, -0.25)	-1.07 (-2.36, 0.23)	-0.01 (-1.47, 1.45), 0.9886	-0.00 (-0.44, 0.43)
Month 18	-0.51 (-1.42, 0.39)	-0.08 (-1.54, 1.37)	-0.43 (-2.08, 1.21), 0.6053	-0.11 (-0.56, 0.34)
≥50	42	13		
Month 9	1.97 (0.74, 3.19)	0.28 (-1.58, 2.13)	1.69 (-0.35, 3.73), 0.1041	0.47 (-0.15, 1.09)
Month 18	2.53 (1.26, 3.80)	1.26 (-0.71, 3.23)	1.27 (-0.90, 3.44), 0.2509	0.31 (-0.32, 0.95)
p-value of Treatment*Baseline NIS	0.1711			

NIS score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurological impairment (range = 0 to 244).
LS estimates and p-value derived from mixed-effects model for repeated measures (MMRM), controlling for categorical factors (treatment, visit), the subgroup variable, continuous covariate (baseline value), and interaction (treatment by visit, treatment by subgroup).
Standardized effect size (d) = LS mean difference/estimated pooled standard deviation with the small sample bias correction.

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Table 16.6
Neuropathy Impairment Score (NIS) Component Scores: Change from Baseline to Month 18, MMRM Model
Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A) Subgroup Analysis
mITT Population

Neuropathy Impairment Score - Sensation (NIS-S)

Subgroup Visit	LS Mean (95% CI) Vutrisiran (HELIOS-A) (N=122)	LS Mean (95% CI) Patisiran (HELIOS-A) (N=42)	LS Mean Difference (Vutrisiran-Patisiran) (95% CI), p-value	Standardized Effect Size (95% CI)
Previous Tetramer Stabilizer Use				
Yes	74	32		
Month 9	-0.12 (-0.90, 0.66)	-0.20 (-1.39, 1.00)	0.07 (-1.35, 1.50), 0.9185	0.02 (-0.39, 0.43)
Month 18	0.45 (-0.43, 1.32)	0.78 (-0.60, 2.16)	-0.34 (-1.97, 1.30), 0.6845	-0.08 (-0.51, 0.34)
No	45	8		
Month 9	0.14 (-0.86, 1.14)	-2.13 (-4.47, 0.21)	2.27 (-0.26, 4.80), 0.0782	0.59 (-0.17, 1.34)
Month 18	0.71 (-0.35, 1.77)	-1.15 (-3.60, 1.29)	1.86 (-0.80, 4.52), 0.1686	0.46 (-0.33, 1.25)
p-value of Treatment*Previous Tetramer Stabilizer Use	0.1299			

NIS score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurological impairment (range = 0 to 244).
LS estimates and p-value derived from mixed-effects model for repeated measures (MMRM), controlling for categorical factors (treatment, visit), the subgroup variable, continuous covariate (baseline value), and interaction (treatment by visit, treatment by subgroup).
Standardized effect size (d) = LS mean difference/estimated pooled standard deviation with the small sample bias correction.

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Table 16.6
Neuropathy Impairment Score (NIS) Component Scores: Change from Baseline to Month 18, MMRM Model
Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A) Subgroup Analysis
mITT Population

Neuropathy Impairment Score - Sensation (NIS-S)

Subgroup Visit	LS Mean (95% CI) Vutrisiran (HELIOS-A) (N=122)	LS Mean (95% CI) Patisiran (HELIOS-A) (N=42)	LS Mean Difference (Vutrisiran-Patisiran) (95% CI), p-value	Standardized Effect Size (95% CI)
Genotype				
V30M	53	20		
Month 9	0.49 (-0.43, 1.41)	-0.97 (-2.47, 0.53)	1.45 (-0.29, 3.20), 0.1017	0.44 (-0.08, 0.95)
Month 18	1.05 (0.06, 2.05)	0.03 (-1.62, 1.67)	1.03 (-0.89, 2.94), 0.2910	0.26 (-0.25, 0.77)
non-V30M	66	20		
Month 9	-0.44 (-1.26, 0.39)	-0.20 (-1.71, 1.31)	-0.24 (-1.95, 1.47), 0.7826	-0.07 (-0.56, 0.43)
Month 18	0.13 (-0.78, 1.04)	0.80 (-0.89, 2.48)	-0.67 (-2.58, 1.24), 0.4905	-0.16 (-0.69, 0.37)
p-value of Treatment*Genotype	0.1639			

NIS score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurological impairment (range = 0 to 244).
LS estimates and p-value derived from mixed-effects model for repeated measures (MMRM), controlling for categorical factors (treatment, visit), the subgroup variable, continuous covariate (baseline value), and interaction (treatment by visit, treatment by subgroup).
Standardized effect size (d) = LS mean difference/estimated pooled standard deviation with the small sample bias correction.

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Table 16.6
Neuropathy Impairment Score (NIS) Component Scores: Change from Baseline to Month 18, MMRM Model
Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A) Subgroup Analysis
mITT Population

Neuropathy Impairment Score - Sensation (NIS-S)

Subgroup Visit	LS Mean (95% CI) Vutrisiran (HELIOS-A) (N=122)	LS Mean (95% CI) Patisiran (HELIOS-A) (N=42)	LS Mean Difference (Vutrisiran-Patisiran) (95% CI), p-value	Standardized Effect Size (95% CI)
FAP Stage				
I	83	30		
Month 9	-0.69 (-1.44, 0.07)	-0.76 (-2.00, 0.47)	0.08 (-1.34, 1.50), 0.9140	0.02 (-0.39, 0.44)
Month 18	-0.11 (-0.94, 0.71)	0.23 (-1.15, 1.61)	-0.34 (-1.93, 1.25), 0.6747	-0.09 (-0.51, 0.33)
II&III	36	10		
Month 9	1.52 (0.36, 2.68)	-0.12 (-2.22, 1.98)	1.64 (-0.68, 3.96), 0.1651	0.53 (-0.16, 1.23)
Month 18	2.09 (0.88, 3.30)	0.87 (-1.35, 3.09)	1.22 (-1.23, 3.67), 0.3267	0.27 (-0.49, 1.02)
p-value of Treatment*FAP Stage	0.2477			

NIS score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurological impairment (range = 0 to 244).
LS estimates and p-value derived from mixed-effects model for repeated measures (MMRM), controlling for categorical factors (treatment, visit), the subgroup variable, continuous covariate (baseline value), and interaction (treatment by visit, treatment by subgroup).
Standardized effect size (d) = LS mean difference/estimated pooled standard deviation with the small sample bias correction.

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Table 16.6
Neuropathy Impairment Score (NIS) Component Scores: Change from Baseline to Month 18, MMRM Model
Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A) Subgroup Analysis
mITT Population

Neuropathy Impairment Score - Sensation (NIS-S)

Subgroup Visit	LS Mean (95% CI) Vutrisiran (HELIOS-A) (N=122)	LS Mean (95% CI) Patisiran (HELIOS-A) (N=42)	LS Mean Difference (Vutrisiran-Patisiran) (95% CI), p-value	Standardized Effect Size (95% CI)
Cardiac Subpopulation				
Yes	38	14		
Month 9	0.11 (-0.96, 1.18)	0.98 (-0.77, 2.73)	-0.88 (-2.92, 1.17), 0.3994	-0.23 (-0.83, 0.38)
Month 18	0.68 (-0.46, 1.81)	1.97 (0.08, 3.85)	-1.29 (-3.49, 0.91), 0.2484	-0.28 (-0.91, 0.34)
No	81	26		
Month 9	-0.09 (-0.83, 0.66)	-1.43 (-2.73, -0.12)	1.34 (-0.16, 2.84), 0.0798	0.42 (-0.03, 0.86)
Month 18	0.48 (-0.36, 1.32)	-0.44 (-1.93, 1.04)	0.93 (-0.77, 2.63), 0.2840	0.25 (-0.21, 0.70)
p-value of Treatment*Cardiac Subpopulation	0.0791			

NIS score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurological impairment (range = 0 to 244).
LS estimates and p-value derived from mixed-effects model for repeated measures (MMRM), controlling for categorical factors (treatment, visit), the subgroup variable, continuous covariate (baseline value), and interaction (treatment by visit, treatment by subgroup).
Standardized effect size (d) = LS mean difference/estimated pooled standard deviation with the small sample bias correction.

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Table 16.6
Neuropathy Impairment Score (NIS) Component Scores: Change from Baseline to Month 18, MMRM Model
Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A) Subgroup Analysis
mITT Population

Neuropathy Impairment Score - Sensation (NIS-S)

Subgroup Visit	LS Mean (95% CI) Vutrisiran (HELIOS-A) (N=122)	LS Mean (95% CI) Patisiran (HELIOS-A) (N=42)	LS Mean Difference (Vutrisiran-Patisiran) (95% CI), p-value	Standardized Effect Size (95% CI)
Weight (kg)				
<65	44	15		
Month 9	0.15 (-0.84, 1.15)	-1.50 (-3.21, 0.21)	1.66 (-0.32, 3.63), 0.1001	0.41 (-0.17, 1.00)
Month 18	0.72 (-0.35, 1.80)	-0.51 (-2.36, 1.33)	1.24 (-0.89, 3.37), 0.2530	0.28 (-0.32, 0.88)
≥65	75	25		
Month 9	-0.13 (-0.91, 0.65)	-0.03 (-1.37, 1.31)	-0.10 (-1.65, 1.45), 0.8959	-0.03 (-0.48, 0.42)
Month 18	0.44 (-0.43, 1.30)	0.96 (-0.56, 2.47)	-0.52 (-2.26, 1.22), 0.5575	-0.13 (-0.60, 0.33)
p-value of Treatment*Weight	0.1582			

NIS score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurological impairment (range = 0 to 244).
LS estimates and p-value derived from mixed-effects model for repeated measures (MMRM), controlling for categorical factors (treatment, visit), the subgroup variable, continuous covariate (baseline value), and interaction (treatment by visit, treatment by subgroup).
Standardized effect size (d) = LS mean difference/estimated pooled standard deviation with the small sample bias correction.

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Table 16.8
Neuropathy Impairment Score (NIS) Components: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Component: Neuropathy Impairment Score - Sensation (NIS-S)

Age (years): <65

Subgroup Visit	Vutrisiran (HELIOS-A) (N=76)	Patisiran (HELIOS-A) (N=31)
Baseline		
n	76	31
Mean (SD)	10.90 (7.09)	10.79 (6.79)
SE	0.81	1.22
Median	9.00	10.50
Min, Max	0.0, 29.0	1.0, 25.5
Month 9		
Actual Value		
n	74	30
Mean (SD)	10.89 (7.42)	9.82 (6.12)
SE	0.86	1.12
Median	9.25	9.00
Min, Max	0.0, 28.0	0.0, 23.0
Change from baseline		
n	74	30
Mean (SD)	-0.01 (3.46)	-0.70 (4.18)
SE	0.40	0.76
Median	0.00	0.00
Min, Max	-10.5, 8.0	-11.0, 8.0

NIS score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurological impairment (range = 0 to 244).

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Table 16.8
Neuropathy Impairment Score (NIS) Components: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Component: Neuropathy Impairment Score - Sensation (NIS-S)

Age (years): <65

Subgroup Visit	Vutrisiran (HELIOS-A) (N=76)	Patisiran (HELIOS-A) (N=31)
Month 18		
Actual Value		
n	74	28
Mean (SD)	11.20 (7.86)	10.75 (6.83)
SE	0.91	1.29
Median	10.25	12.00
Min, Max	0.0, 30.0	0.0, 28.0
Change from baseline		
n	74	28
Mean (SD)	0.28 (3.72)	0.36 (4.40)
SE	0.43	0.83
Median	0.00	0.75
Min, Max	-11.0, 8.0	-10.0, 10.0

NIS score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurological impairment (range = 0 to 244).

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Table 16.8
Neuropathy Impairment Score (NIS) Components: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Component: Neuropathy Impairment Score - Sensation (NIS-S)

Age (years): ≥65

Subgroup Visit	Vutrisiran (HELIOS-A) (N=46)	Patisiran (HELIOS-A) (N=11)
Baseline		
n	46	11
Mean (SD)	13.25 (7.02)	14.14 (7.61)
SE	1.04	2.29
Median	13.25	14.50
Min, Max	3.0, 29.0	4.0, 29.5
Month 9		
Actual Value		
n	43	10
Mean (SD)	13.14 (7.94)	13.85 (7.57)
SE	1.21	2.39
Median	12.00	13.50
Min, Max	1.0, 29.5	4.5, 30.0
Change from baseline		
n	43	10
Mean (SD)	-0.09 (3.11)	-0.10 (3.55)
SE	0.47	1.12
Median	0.00	0.25
Min, Max	-11.5, 6.5	-6.5, 5.0

NIS score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurological impairment (range = 0 to 244).

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Table 16.8
Neuropathy Impairment Score (NIS) Components: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Component: Neuropathy Impairment Score - Sensation (NIS-S)

Age (years): ≥65

Subgroup Visit	Vutrisiran (HELIOS-A) (N=46)	Patisiran (HELIOS-A) (N=11)
Month 18		
Actual Value		
n	41	9
Mean (SD)	14.55 (7.43)	15.11 (7.00)
SE	1.16	2.33
Median	13.00	14.50
Min, Max	3.5, 31.0	6.0, 29.0
Change from baseline		
n	41	9
Mean (SD)	1.02 (4.55)	0.28 (3.78)
SE	0.71	1.26
Median	1.00	-0.50
Min, Max	-10.0, 12.0	-3.5, 6.0

NIS score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurological impairment (range = 0 to 244).

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Table 16.8
Neuropathy Impairment Score (NIS) Components: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Component: Neuropathy Impairment Score - Sensation (NIS-S)

Sex: Male

Subgroup Visit	Vutrisiran (HELIOS-A) (N=79)	Patisiran (HELIOS-A) (N=27)
Baseline		
n	79	27
Mean (SD)	12.69 (7.12)	12.20 (6.34)
SE	0.80	1.22
Median	13.00	11.50
Min, Max	0.0, 29.0	1.0, 25.5
Month 9		
Actual Value		
n	76	25
Mean (SD)	12.45 (7.72)	11.70 (6.32)
SE	0.89	1.26
Median	12.00	12.00
Min, Max	0.5, 27.5	0.0, 23.0
Change from baseline		
n	76	25
Mean (SD)	-0.16 (3.40)	-0.08 (3.94)
SE	0.39	0.79
Median	0.00	0.00
Min, Max	-11.5, 8.0	-9.0, 8.0

NIS score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurological impairment (range = 0 to 244).

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Table 16.8
Neuropathy Impairment Score (NIS) Components: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Component: Neuropathy Impairment Score - Sensation (NIS-S)

Sex: Male

Subgroup Visit	Vutrisiran (HELIOS-A) (N=79)	Patisiran (HELIOS-A) (N=27)
Month 18		
Actual Value		
n	74	23
Mean (SD)	13.19 (7.75)	12.39 (6.79)
SE	0.90	1.42
Median	13.00	13.00
Min, Max	0.0, 31.0	0.0, 28.0
Change from baseline		
n	74	23
Mean (SD)	0.55 (4.12)	0.72 (4.22)
SE	0.48	0.88
Median	0.00	0.50
Min, Max	-10.0, 10.0	-5.5, 10.0

NIS score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurological impairment (range = 0 to 244).

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Table 16.8
Neuropathy Impairment Score (NIS) Components: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Component: Neuropathy Impairment Score - Sensation (NIS-S)

Sex: Female

Subgroup Visit	Vutrisiran (HELIOS-A) (N=43)	Patisiran (HELIOS-A) (N=15)
Baseline		
n	43	15
Mean (SD)	10.13 (6.92)	10.70 (8.39)
SE	1.06	2.17
Median	8.00	10.50
Min, Max	2.0, 29.0	1.5, 29.5
Month 9		
Actual Value		
n	41	15
Mean (SD)	10.35 (7.46)	9.37 (7.15)
SE	1.16	1.85
Median	8.50	8.00
Min, Max	0.0, 29.5	0.0, 30.0
Change from baseline		
n	41	15
Mean (SD)	0.18 (3.19)	-1.33 (4.10)
SE	0.50	1.06
Median	0.00	-0.50
Min, Max	-9.0, 8.0	-11.0, 4.0

NIS score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurological impairment (range = 0 to 244).

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Table 16.8
Neuropathy Impairment Score (NIS) Components: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Component: Neuropathy Impairment Score - Sensation (NIS-S)

Sex: Female

Subgroup Visit	Vutrisiran (HELIOS-A) (N=43)	Patisiran (HELIOS-A) (N=15)
Month 18		
Actual Value		
n	41	14
Mean (SD)	10.96 (7.89)	10.86 (7.59)
SE	1.23	2.03
Median	9.00	10.00
Min, Max	0.0, 28.0	0.5, 29.0
Change from baseline		
n	41	14
Mean (SD)	0.55 (3.91)	-0.29 (4.28)
SE	0.61	1.14
Median	0.00	0.75
Min, Max	-11.0, 12.0	-10.0, 4.5

NIS score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurological impairment (range = 0 to 244).

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

Alnylam Pharmaceuticals Inc.
ALN-TTRSC02-002

Table 16.8
Neuropathy Impairment Score (NIS) Components: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Component: Neuropathy Impairment Score - Sensation (NIS-S)

Race: White

Subgroup Visit	Vutrisiran (HELIOS-A) (N=86)	Patisiran (HELIOS-A) (N=29)
Baseline		
n	86	29
Mean (SD)	12.26 (6.98)	13.12 (6.48)
SE	0.75	1.20
Median	11.50	13.00
Min, Max	2.0, 29.0	2.5, 29.5
Month 9		
Actual Value		
n	83	28
Mean (SD)	12.13 (7.54)	12.30 (6.32)
SE	0.83	1.19
Median	11.00	11.75
Min, Max	1.0, 29.5	2.0, 30.0
Change from baseline		
n	83	28
Mean (SD)	-0.08 (3.49)	-0.71 (4.23)
SE	0.38	0.80
Median	0.00	0.00
Min, Max	-11.5, 8.0	-11.0, 8.0

NIS score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurological impairment (range = 0 to 244).

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Alnylam Pharmaceuticals Inc.
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Table 16.8
Neuropathy Impairment Score (NIS) Components: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Component: Neuropathy Impairment Score - Sensation (NIS-S)

Race: White

Subgroup Visit	Vutrisiran (HELIOS-A) (N=86)	Patisiran (HELIOS-A) (N=29)
Month 18		
Actual Value		
n	82	26
Mean (SD)	12.97 (7.58)	13.52 (6.45)
SE	0.84	1.27
Median	12.75	13.00
Min, Max	0.0, 31.0	3.0, 29.0
Change from baseline		
n	82	26
Mean (SD)	0.68 (4.06)	0.44 (4.54)
SE	0.45	0.89
Median	0.00	0.75
Min, Max	-11.0, 12.0	-10.0, 10.0

NIS score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurological impairment (range = 0 to 244).

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Alnylam Pharmaceuticals Inc.
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Table 16.8
Neuropathy Impairment Score (NIS) Components: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Component: Neuropathy Impairment Score - Sensation (NIS-S)

Race: All Other Races

Subgroup Visit	Vutrisiran (HELIOS-A) (N=36)	Patisiran (HELIOS-A) (N=13)
Baseline		
n	36	13
Mean (SD)	10.67 (7.46)	8.42 (7.52)
SE	1.24	2.09
Median	7.00	6.00
Min, Max	0.0, 25.0	1.0, 21.5
Month 9		
Actual Value		
n	34	12
Mean (SD)	10.72 (7.98)	7.38 (6.35)
SE	1.37	1.83
Median	8.50	6.00
Min, Max	0.0, 28.0	0.0, 22.0
Change from baseline		
n	34	12
Mean (SD)	0.06 (2.92)	-0.17 (3.54)
SE	0.50	1.02
Median	0.00	0.25
Min, Max	-7.0, 8.0	-6.0, 5.0

NIS score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurological impairment (range = 0 to 244).

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Table 16.8
Neuropathy Impairment Score (NIS) Components: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Component: Neuropathy Impairment Score - Sensation (NIS-S)

Race: All Other Races

Subgroup Visit	Vutrisiran (HELIOS-A) (N=36)	Patisiran (HELIOS-A) (N=13)
Month 18		
Actual Value		
n	33	11
Mean (SD)	10.97 (8.42)	7.77 (6.98)
SE	1.47	2.10
Median	8.00	6.50
Min, Max	0.0, 30.0	0.0, 19.5
Change from baseline		
n	33	11
Mean (SD)	0.21 (4.00)	0.09 (3.48)
SE	0.70	1.05
Median	0.00	0.50
Min, Max	-10.0, 10.0	-5.5, 6.0

NIS score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurological impairment (range = 0 to 244).

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

Alnylam Pharmaceuticals Inc.
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Table 16.8
Neuropathy Impairment Score (NIS) Components: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Component: Neuropathy Impairment Score - Sensation (NIS-S)

Region: North America

Subgroup Visit	Vutrisiran (HELIOS-A) (N=27)	Patisiran (HELIOS-A) (N=8)
Baseline		
n	27	8
Mean (SD)	6.63 (5.00)	6.81 (4.91)
SE	0.96	1.73
Median	4.00	6.00
Min, Max	2.0, 20.0	2.5, 18.0
Month 9		
Actual Value		
n	25	8
Mean (SD)	5.32 (4.52)	6.25 (2.67)
SE	0.90	0.94
Median	4.00	6.25
Min, Max	1.0, 21.5	2.0, 11.0
Change from baseline		
n	25	8
Mean (SD)	-0.52 (2.88)	-0.56 (4.80)
SE	0.58	1.70
Median	0.00	-0.25
Min, Max	-9.0, 5.0	-11.0, 5.0

NIS score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurological impairment (range = 0 to 244).

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Table 16.8
Neuropathy Impairment Score (NIS) Components: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Component: Neuropathy Impairment Score - Sensation (NIS-S)

Region: North America

Subgroup Visit	Vutrisiran (HELIOS-A) (N=27)	Patisiran (HELIOS-A) (N=8)
Month 18		
Actual Value		
n	25	6
Mean (SD)	8.40 (6.37)	7.75 (4.42)
SE	1.27	1.81
Median	6.00	7.25
Min, Max	0.0, 21.5	3.0, 13.0
Change from baseline		
n	25	6
Mean (SD)	1.60 (4.50)	0.42 (4.95)
SE	0.90	2.02
Median	1.50	0.75
Min, Max	-11.0, 10.0	-8.0, 6.0

NIS score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurological impairment (range = 0 to 244).

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Table 16.8
Neuropathy Impairment Score (NIS) Components: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Component: Neuropathy Impairment Score - Sensation (NIS-S)

Region: Western Europe

Subgroup Visit	Vutrisiran (HELIOS-A) (N=42)	Patisiran (HELIOS-A) (N=20)
Baseline		
n	42	20
Mean (SD)	13.71 (7.05)	14.68 (6.02)
SE	1.09	1.35
Median	13.50	14.25
Min, Max	4.0, 29.0	4.0, 29.5
Month 9		
Actual Value		
n	40	18
Mean (SD)	14.09 (7.24)	13.33 (5.80)
SE	1.15	1.37
Median	14.00	13.00
Min, Max	4.0, 29.5	4.5, 30.0
Change from baseline		
n	40	18
Mean (SD)	0.33 (3.07)	-1.03 (4.47)
SE	0.49	1.05
Median	0.00	-0.25
Min, Max	-7.0, 8.0	-9.0, 8.0

NIS score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurological impairment (range = 0 to 244).

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Table 16.8
Neuropathy Impairment Score (NIS) Components: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Component: Neuropathy Impairment Score - Sensation (NIS-S)

Region: Western Europe

Subgroup Visit	Vutrisiran (HELIOS-A) (N=42)	Patisiran (HELIOS-A) (N=20)
Month 18		
Actual Value		
n	40	18
Mean (SD)	13.96 (7.13)	14.31 (5.41)
SE	1.13	1.28
Median	13.25	13.75
Min, Max	2.5, 31.0	6.0, 29.0
Change from baseline		
n	40	18
Mean (SD)	0.20 (3.11)	-0.06 (4.27)
SE	0.49	1.01
Median	-0.25	0.00
Min, Max	-4.5, 6.5	-10.0, 7.0

NIS score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurological impairment (range = 0 to 244).

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Table 16.8
Neuropathy Impairment Score (NIS) Components: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Component: Neuropathy Impairment Score - Sensation (NIS-S)

Region: Rest of World

Subgroup Visit	Vutrisiran (HELIOS-A) (N=53)	Patisiran (HELIOS-A) (N=14)
Baseline		
n	53	14
Mean (SD)	12.89 (6.98)	10.14 (7.82)
SE	0.96	2.09
Median	13.50	8.50
Min, Max	0.0, 25.0	1.0, 21.5
Month 9		
Actual Value		
n	52	14
Mean (SD)	12.97 (7.60)	10.21 (7.93)
SE	1.05	2.12
Median	12.50	8.75
Min, Max	0.0, 28.0	0.0, 22.0
Change from baseline		
n	52	14
Mean (SD)	-0.10 (3.70)	0.07 (2.94)
SE	0.51	0.79
Median	0.00	0.75
Min, Max	-11.5, 8.0	-6.0, 4.0

NIS score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurological impairment (range = 0 to 244).

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Table 16.8
Neuropathy Impairment Score (NIS) Components: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Component: Neuropathy Impairment Score - Sensation (NIS-S)

Region: Rest of World

Subgroup Visit	Vutrisiran (HELIOS-A) (N=53)	Patisiran (HELIOS-A) (N=14)
Month 18		
Actual Value		
n	50	13
Mean (SD)	13.14 (8.49)	10.23 (8.86)
SE	1.20	2.46
Median	12.25	7.00
Min, Max	0.0, 30.0	0.0, 28.0
Change from baseline		
n	50	13
Mean (SD)	0.30 (4.41)	0.85 (4.07)
SE	0.62	1.13
Median	-0.25	1.00
Min, Max	-10.0, 12.0	-5.5, 10.0

NIS score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurological impairment (range = 0 to 244).

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Table 16.8
Neuropathy Impairment Score (NIS) Components: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Component: Neuropathy Impairment Score - Sensation (NIS-S)

Baseline NIS: <50

Subgroup Visit	Vutrisiran (HELIOS-A) (N=78)	Patisiran (HELIOS-A) (N=27)
Baseline		
n	78	27
Mean (SD)	7.94 (4.66)	8.48 (5.36)
SE	0.53	1.03
Median	6.50	8.00
Min, Max	0.0, 20.0	1.0, 20.0
Month 9		
Actual Value		
n	77	27
Mean (SD)	7.73 (5.01)	8.13 (5.03)
SE	0.57	0.97
Median	6.50	7.50
Min, Max	0.0, 22.5	0.0, 23.0
Change from baseline		
n	77	27
Mean (SD)	-0.27 (3.08)	-0.35 (4.26)
SE	0.35	0.82
Median	0.00	-0.50
Min, Max	-9.0, 8.0	-11.0, 8.0

NIS score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurological impairment (range = 0 to 244).

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Table 16.8
Neuropathy Impairment Score (NIS) Components: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Component: Neuropathy Impairment Score - Sensation (NIS-S)

Baseline NIS: <50

Subgroup Visit	Vutrisiran (HELIOS-A) (N=78)	Patisiran (HELIOS-A) (N=27)
Month 18		
Actual Value		
n	75	25
Mean (SD)	8.27 (5.38)	9.14 (5.40)
SE	0.62	1.08
Median	7.50	10.00
Min, Max	0.0, 21.5	0.0, 20.0
Change from baseline		
n	75	25
Mean (SD)	0.19 (3.89)	0.40 (4.30)
SE	0.45	0.86
Median	0.00	0.50
Min, Max	-11.0, 10.0	-10.0, 7.0

NIS score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurological impairment (range = 0 to 244).

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Table 16.8
Neuropathy Impairment Score (NIS) Components: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Component: Neuropathy Impairment Score - Sensation (NIS-S)

Baseline NIS: ≥50

Subgroup Visit	Vutrisiran (HELIOS-A) (N=44)	Patisiran (HELIOS-A) (N=15)
Baseline		
n	44	15
Mean (SD)	18.61 (5.45)	17.40 (6.19)
SE	0.82	1.60
Median	19.00	18.00
Min, Max	4.0, 29.0	2.5, 29.5
Month 9		
Actual Value		
n	40	13
Mean (SD)	19.40 (5.81)	16.42 (6.22)
SE	0.92	1.73
Median	19.75	14.50
Min, Max	2.5, 29.5	4.0, 30.0
Change from baseline		
n	40	13
Mean (SD)	0.39 (3.73)	-0.96 (3.50)
SE	0.59	0.97
Median	0.75	0.50
Min, Max	-11.5, 6.5	-9.0, 3.0

NIS score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurological impairment (range = 0 to 244).

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Table 16.8
Neuropathy Impairment Score (NIS) Components: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Component: Neuropathy Impairment Score - Sensation (NIS-S)

Baseline NIS: ≥50

Subgroup Visit	Vutrisiran (HELIOS-A) (N=44)	Patisiran (HELIOS-A) (N=15)
Month 18		
Actual Value		
n	40	12
Mean (SD)	20.13 (5.56)	17.38 (6.96)
SE	0.88	2.01
Median	20.00	17.75
Min, Max	7.0, 31.0	3.5, 29.0
Change from baseline		
n	40	12
Mean (SD)	1.23 (4.24)	0.21 (4.20)
SE	0.67	1.21
Median	0.50	0.25
Min, Max	-8.0, 12.0	-5.0, 10.0

NIS score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurological impairment (range = 0 to 244).

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Table 16.8
Neuropathy Impairment Score (NIS) Components: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Component: Neuropathy Impairment Score - Sensation (NIS-S)

Previous Tetramer Stabilizer Use: Yes

Subgroup Visit	Vutrisiran (HELIOS-A) (N=75)	Patisiran (HELIOS-A) (N=33)
Baseline		
n	75	33
Mean (SD)	12.69 (7.02)	12.47 (7.34)
SE	0.81	1.28
Median	13.00	13.00
Min, Max	2.0, 29.0	1.0, 29.5
Month 9		
Actual Value		
n	74	32
Mean (SD)	12.51 (7.66)	12.08 (6.61)
SE	0.89	1.17
Median	11.50	12.25
Min, Max	1.0, 27.5	2.0, 30.0
Change from baseline		
n	74	32
Mean (SD)	-0.08 (3.02)	-0.19 (3.81)
SE	0.35	0.67
Median	0.00	0.50
Min, Max	-9.0, 6.5	-9.0, 8.0

NIS score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurological impairment (range = 0 to 244).

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Table 16.8
Neuropathy Impairment Score (NIS) Components: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Component: Neuropathy Impairment Score - Sensation (NIS-S)

Previous Tetramer Stabilizer Use: Yes

Subgroup Visit	Vutrisiran (HELIOS-A) (N=75)	Patisiran (HELIOS-A) (N=33)
Month 18		
Actual Value		
n	71	30
Mean (SD)	12.68 (7.88)	12.80 (7.01)
SE	0.93	1.28
Median	12.00	13.25
Min, Max	0.0, 31.0	1.0, 29.0
Change from baseline		
n	71	30
Mean (SD)	0.14 (4.09)	0.53 (4.05)
SE	0.49	0.74
Median	0.00	0.75
Min, Max	-11.0, 12.0	-10.0, 10.0

NIS score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurological impairment (range = 0 to 244).

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Table 16.8
Neuropathy Impairment Score (NIS) Components: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Component: Neuropathy Impairment Score - Sensation (NIS-S)

Previous Tetramer Stabilizer Use: No

Subgroup Visit	Vutrisiran (HELIOS-A) (N=47)	Patisiran (HELIOS-A) (N=9)
Baseline		
n	47	9
Mean (SD)	10.34 (7.14)	8.72 (5.35)
SE	1.04	1.78
Median	8.00	6.00
Min, Max	0.0, 29.0	1.5, 18.0
Month 9		
Actual Value		
n	43	8
Mean (SD)	10.36 (7.57)	5.81 (4.11)
SE	1.15	1.45
Median	9.50	6.25
Min, Max	0.0, 29.5	0.0, 11.0
Change from baseline		
n	43	8
Mean (SD)	0.02 (3.81)	-2.00 (4.64)
SE	0.58	1.64
Median	0.00	-1.00
Min, Max	-11.5, 8.0	-11.0, 5.0

NIS score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurological impairment (range = 0 to 244).

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Table 16.8
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mITT Population

Component: Neuropathy Impairment Score - Sensation (NIS-S)

Previous Tetramer Stabilizer Use: No

Subgroup Visit	Vutrisiran (HELIOS-A) (N=47)	Patisiran (HELIOS-A) (N=9)
Month 18		
Actual Value		
n	44	7
Mean (SD)	11.94 (7.85)	7.57 (5.79)
SE	1.18	2.19
Median	9.75	10.00
Min, Max	0.0, 28.0	0.0, 13.0
Change from baseline		
n	44	7
Mean (SD)	1.20 (3.88)	-0.50 (5.10)
SE	0.59	1.93
Median	0.50	-1.00
Min, Max	-8.0, 10.0	-8.0, 6.0

NIS score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurological impairment (range = 0 to 244).

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Table 16.8
Neuropathy Impairment Score (NIS) Components: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Component: Neuropathy Impairment Score - Sensation (NIS-S)

Genotype: V30M

Subgroup Visit	Vutrisiran (HELIOS-A) (N=54)	Patisiran (HELIOS-A) (N=20)
Baseline		
n	54	20
Mean (SD)	13.25 (7.00)	14.70 (6.50)
SE	0.95	1.45
Median	14.50	14.25
Min, Max	2.0, 29.0	2.0, 29.5
Month 9		
Actual Value		
n	52	20
Mean (SD)	13.54 (7.25)	13.45 (6.04)
SE	1.01	1.35
Median	14.00	13.00
Min, Max	2.0, 25.5	5.0, 30.0
Change from baseline		
n	52	20
Mean (SD)	0.52 (2.84)	-1.25 (4.61)
SE	0.39	1.03
Median	0.00	-0.50
Min, Max	-6.0, 8.0	-11.0, 8.0

NIS score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurological impairment (range = 0 to 244).

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Table 16.8
Neuropathy Impairment Score (NIS) Components: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Component: Neuropathy Impairment Score - Sensation (NIS-S)

Genotype: V30M

Subgroup Visit	Vutrisiran (HELIOS-A) (N=54)	Patisiran (HELIOS-A) (N=20)
Month 18		
Actual Value		
n	52	20
Mean (SD)	13.67 (7.61)	14.58 (5.18)
SE	1.06	1.16
Median	13.50	13.75
Min, Max	2.0, 31.0	6.5, 29.0
Change from baseline		
n	52	20
Mean (SD)	0.70 (3.87)	-0.13 (4.51)
SE	0.54	1.01
Median	0.00	0.25
Min, Max	-10.0, 12.0	-10.0, 7.0

NIS score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurological impairment (range = 0 to 244).

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

Alnylam Pharmaceuticals Inc.
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Table 16.8
Neuropathy Impairment Score (NIS) Components: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Component: Neuropathy Impairment Score - Sensation (NIS-S)

Genotype: non-V30M

Subgroup Visit	Vutrisiran (HELIOS-A) (N=68)	Patisiran (HELIOS-A) (N=22)
Baseline		
n	68	22
Mean (SD)	10.63 (7.07)	8.91 (6.54)
SE	0.86	1.39
Median	8.75	6.00
Min, Max	0.0, 29.0	1.0, 20.0
Month 9		
Actual Value		
n	65	20
Mean (SD)	10.26 (7.72)	8.20 (6.31)
SE	0.96	1.41
Median	8.00	6.75
Min, Max	0.0, 29.5	0.0, 21.0
Change from baseline		
n	65	20
Mean (SD)	-0.49 (3.62)	0.15 (3.24)
SE	0.45	0.73
Median	0.00	0.75
Min, Max	-11.5, 8.0	-6.5, 5.0

NIS score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurological impairment (range = 0 to 244).

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

Alnylam Pharmaceuticals Inc.
ALN-TTRSC02-002

Table 16.8
Neuropathy Impairment Score (NIS) Components: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Component: Neuropathy Impairment Score - Sensation (NIS-S)

Genotype: non-V30M

Subgroup Visit	Vutrisiran (HELIOS-A) (N=68)	Patisiran (HELIOS-A) (N=22)
Month 18		
Actual Value		
n	63	17
Mean (SD)	11.34 (7.93)	8.56 (7.67)
SE	1.00	1.86
Median	9.00	6.00
Min, Max	0.0, 30.0	0.0, 28.0
Change from baseline		
n	63	17
Mean (SD)	0.42 (4.18)	0.88 (3.89)
SE	0.53	0.94
Median	0.00	0.50
Min, Max	-11.0, 10.0	-5.5, 10.0

NIS score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurological impairment (range = 0 to 244).

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

Alnylam Pharmaceuticals Inc.
ALN-TTRSC02-002

Table 16.8
Neuropathy Impairment Score (NIS) Components: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Component: Neuropathy Impairment Score - Sensation (NIS-S)

FAP Stage: I

Subgroup Visit	Vutrisiran (HELIOS-A) (N=84)	Patisiran (HELIOS-A) (N=31)
Baseline		
n	84	31
Mean (SD)	9.63 (6.14)	9.52 (5.84)
SE	0.67	1.05
Median	8.00	10.00
Min, Max	0.0, 24.0	1.0, 21.5
Month 9		
Actual Value		
n	82	30
Mean (SD)	9.29 (6.66)	8.98 (5.65)
SE	0.74	1.03
Median	7.00	8.25
Min, Max	0.0, 27.5	0.0, 23.0
Change from baseline		
n	82	30
Mean (SD)	-0.31 (3.50)	-0.32 (3.96)
SE	0.39	0.72
Median	0.00	0.25
Min, Max	-11.5, 8.0	-11.0, 8.0

NIS score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurological impairment (range = 0 to 244).

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

Alnylam Pharmaceuticals Inc.
ALN-TTRSC02-002

Table 16.8
Neuropathy Impairment Score (NIS) Components: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Component: Neuropathy Impairment Score - Sensation (NIS-S)

FAP Stage: I

Subgroup Visit	Vutrisiran (HELIOS-A) (N=84)	Patisiran (HELIOS-A) (N=31)
Month 18		
Actual Value		
n	81	29
Mean (SD)	9.66 (6.50)	9.72 (5.71)
SE	0.72	1.06
Median	8.00	10.00
Min, Max	0.0, 23.0	0.0, 20.0
Change from baseline		
n	81	29
Mean (SD)	0.03 (3.67)	0.26 (3.98)
SE	0.41	0.74
Median	0.00	0.50
Min, Max	-11.0, 9.0	-10.0, 7.0

NIS score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurological impairment (range = 0 to 244).

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

Alnylam Pharmaceuticals Inc.
ALN-TTRSC02-002

Table 16.8
Neuropathy Impairment Score (NIS) Components: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Component: Neuropathy Impairment Score - Sensation (NIS-S)

FAP Stage: II&III

Subgroup Visit	Vutrisiran (HELIOS-A) (N=38)	Patisiran (HELIOS-A) (N=11)
Baseline		
n	38	11
Mean (SD)	16.55 (6.91)	17.73 (6.95)
SE	1.12	2.10
Median	17.00	18.00
Min, Max	4.0, 29.0	6.0, 29.5
Month 9		
Actual Value		
n	35	10
Mean (SD)	17.40 (6.87)	16.35 (6.61)
SE	1.16	2.09
Median	18.00	15.50
Min, Max	4.0, 29.5	6.0, 30.0
Change from baseline		
n	35	10
Mean (SD)	0.59 (2.80)	-1.25 (4.23)
SE	0.47	1.34
Median	0.50	0.00
Min, Max	-6.0, 6.5	-9.0, 5.0

NIS score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurological impairment (range = 0 to 244).

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

Alnylam Pharmaceuticals Inc.
ALN-TTRSC02-002

Table 16.8
Neuropathy Impairment Score (NIS) Components: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Component: Neuropathy Impairment Score - Sensation (NIS-S)

FAP Stage: II&III

Subgroup Visit	Vutrisiran (HELIOS-A) (N=38)	Patisiran (HELIOS-A) (N=11)
Month 18		
Actual Value		
n	34	8
Mean (SD)	18.91 (6.92)	19.38 (6.37)
SE	1.19	2.25
Median	19.75	18.50
Min, Max	7.0, 31.0	12.0, 29.0
Change from baseline		
n	34	8
Mean (SD)	1.78 (4.61)	0.63 (5.26)
SE	0.79	1.86
Median	0.50	0.25
Min, Max	-10.0, 12.0	-5.0, 10.0

NIS score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurological impairment (range = 0 to 244).

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

Alnylam Pharmaceuticals Inc.
ALN-TTRSC02-002

Table 16.8
Neuropathy Impairment Score (NIS) Components: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Component: Neuropathy Impairment Score - Sensation (NIS-S)

Cardiac Subpopulation: Yes

Subgroup Visit	Vutrisiran (HELIOS-A) (N=40)	Patisiran (HELIOS-A) (N=14)
Baseline		
n	40	14
Mean (SD)	13.29 (7.12)	12.68 (8.35)
SE	1.13	2.23
Median	13.50	13.75
Min, Max	2.0, 29.0	1.0, 29.5
Month 9		
Actual Value		
n	38	14
Mean (SD)	13.82 (7.81)	13.64 (7.34)
SE	1.27	1.96
Median	14.50	13.50
Min, Max	2.0, 28.0	2.0, 30.0
Change from baseline		
n	38	14
Mean (SD)	0.05 (4.16)	0.96 (2.89)
SE	0.67	0.77
Median	0.50	1.00
Min, Max	-11.5, 6.5	-6.0, 5.0

NIS score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurological impairment (range = 0 to 244).

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

Alnylam Pharmaceuticals Inc.
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Table 16.8
Neuropathy Impairment Score (NIS) Components: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Component: Neuropathy Impairment Score - Sensation (NIS-S)

Cardiac Subpopulation: Yes

Subgroup Visit	Vutrisiran (HELIOS-A) (N=40)	Patisiran (HELIOS-A) (N=14)
Month 18		
Actual Value		
n	37	13
Mean (SD)	13.93 (8.15)	13.92 (8.86)
SE	1.34	2.46
Median	13.00	13.50
Min, Max	0.0, 30.0	1.0, 29.0
Change from baseline		
n	37	13
Mean (SD)	0.26 (4.73)	1.81 (4.00)
SE	0.78	1.11
Median	0.00	1.00
Min, Max	-11.0, 8.0	-5.0, 10.0

NIS score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurological impairment (range = 0 to 244).

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

Alnylam Pharmaceuticals Inc.
ALN-TTRSC02-002

Table 16.8
Neuropathy Impairment Score (NIS) Components: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Component: Neuropathy Impairment Score - Sensation (NIS-S)

Cardiac Subpopulation: No

Subgroup Visit	Vutrisiran (HELIOS-A) (N=82)	Patisiran (HELIOS-A) (N=28)
Baseline		
n	82	28
Mean (SD)	11.05 (7.06)	11.16 (6.46)
SE	0.78	1.22
Median	9.50	10.75
Min, Max	0.0, 29.0	1.5, 25.5
Month 9		
Actual Value		
n	79	26
Mean (SD)	10.71 (7.43)	9.31 (5.84)
SE	0.84	1.15
Median	8.50	8.25
Min, Max	0.0, 29.5	0.0, 23.0
Change from baseline		
n	79	26
Mean (SD)	-0.09 (2.86)	-1.37 (4.31)
SE	0.32	0.85
Median	0.00	-0.50
Min, Max	-7.5, 8.0	-11.0, 8.0

NIS score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurological impairment (range = 0 to 244).

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

Alnylam Pharmaceuticals Inc.
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Table 16.8
Neuropathy Impairment Score (NIS) Components: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Component: Neuropathy Impairment Score - Sensation (NIS-S)

Cardiac Subpopulation: No

Subgroup Visit	Vutrisiran (HELIOS-A) (N=82)	Patisiran (HELIOS-A) (N=28)
Month 18		
Actual Value		
n	78	24
Mean (SD)	11.67 (7.64)	10.67 (5.71)
SE	0.86	1.17
Median	10.25	12.00
Min, Max	0.0, 31.0	0.0, 21.0
Change from baseline		
n	78	24
Mean (SD)	0.69 (3.68)	-0.46 (4.19)
SE	0.42	0.85
Median	0.00	-0.25
Min, Max	-7.5, 12.0	-10.0, 7.0

NIS score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurological impairment (range = 0 to 244).

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

Alnylam Pharmaceuticals Inc.
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Table 16.8
Neuropathy Impairment Score (NIS) Components: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Component: Neuropathy Impairment Score - Sensation (NIS-S)

Weight (kg): <65

Subgroup Visit	Vutrisiran (HELIOS-A) (N=46)	Patisiran (HELIOS-A) (N=15)
Baseline		
n	46	15
Mean (SD)	12.52 (7.48)	12.50 (8.28)
SE	1.10	2.14
Median	12.50	11.00
Min, Max	2.0, 29.0	2.0, 29.5
Month 9		
Actual Value		
n	44	15
Mean (SD)	13.19 (7.94)	10.97 (7.67)
SE	1.20	1.98
Median	11.50	8.50
Min, Max	2.0, 28.0	0.0, 30.0
Change from baseline		
n	44	15
Mean (SD)	0.30 (3.59)	-1.53 (5.26)
SE	0.54	1.36
Median	1.00	-0.50
Min, Max	-11.5, 6.5	-11.0, 8.0

NIS score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurological impairment (range = 0 to 244).

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

Alnylam Pharmaceuticals Inc.
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Table 16.8
Neuropathy Impairment Score (NIS) Components: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Component: Neuropathy Impairment Score - Sensation (NIS-S)

Weight (kg): <65

Subgroup Visit	Vutrisiran (HELIOS-A) (N=46)	Patisiran (HELIOS-A) (N=15)
Month 18		
Actual Value		
n	42	14
Mean (SD)	12.81 (8.00)	12.18 (7.51)
SE	1.23	2.01
Median	11.75	11.25
Min, Max	0.0, 30.0	0.0, 29.0
Change from baseline		
n	42	14
Mean (SD)	0.19 (4.42)	-0.89 (4.57)
SE	0.68	1.22
Median	0.00	0.75
Min, Max	-11.0, 8.0	-10.0, 4.5

NIS score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurological impairment (range = 0 to 244).

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

Alnylam Pharmaceuticals Inc.
ALN-TTRSC02-002

Table 16.8
Neuropathy Impairment Score (NIS) Components: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Component: Neuropathy Impairment Score - Sensation (NIS-S)

Weight (kg): ≥65

Subgroup Visit	Vutrisiran (HELIOS-A) (N=76)	Patisiran (HELIOS-A) (N=27)
Baseline		
n	76	27
Mean (SD)	11.34 (6.92)	11.20 (6.44)
SE	0.79	1.24
Median	10.00	11.00
Min, Max	0.0, 29.0	1.0, 21.5
Month 9		
Actual Value		
n	73	25
Mean (SD)	10.83 (7.41)	10.74 (6.13)
SE	0.87	1.23
Median	9.00	11.00
Min, Max	0.0, 29.5	0.0, 22.0
Change from baseline		
n	73	25
Mean (SD)	-0.25 (3.15)	0.04 (2.97)
SE	0.37	0.59
Median	0.00	0.00
Min, Max	-10.5, 8.0	-6.5, 5.0

NIS score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurological impairment (range = 0 to 244).

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

Alnylam Pharmaceuticals Inc.
ALN-TTRSC02-002

Table 16.8
Neuropathy Impairment Score (NIS) Components: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Component: Neuropathy Impairment Score - Sensation (NIS-S)

Weight (kg): ≥65

Subgroup Visit	Vutrisiran (HELIOS-A) (N=76)	Patisiran (HELIOS-A) (N=27)
Month 18		
Actual Value		
n	73	23
Mean (SD)	12.16 (7.80)	11.59 (6.90)
SE	0.91	1.44
Median	12.00	13.00
Min, Max	0.0, 31.0	0.5, 28.0
Change from baseline		
n	73	23
Mean (SD)	0.75 (3.81)	1.09 (3.89)
SE	0.45	0.81
Median	0.00	0.50
Min, Max	-8.0, 12.0	-5.0, 10.0

NIS score = mean of 2 nonmissing assessments planned to be performed ≥24 hours to ≤7 days apart at each scheduled visit, after component imputation; lower scores indicate less neurological impairment (range = 0 to 244).

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

Subgruppenanalysen zum Endpunkt „Veränderung des Ernährungszustandes gemessen anhand des mBMI“

Alnylam Pharmaceuticals Inc.
ALN-TTRSC02-002

Table 5.2
Modified Body Mass Index (mBMI): Change from Baseline to Month 18, MMRM Model
Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A) Subgroup Analysis
mITT Population

Subgroup Visit	LS Mean (95% CI) Vutrisiran (HELIOS-A) (N=122)	LS Mean (95% CI) Patisiran (HELIOS-A) (N=42)	LS Mean Difference (Vutrisiran-Patisiran) (95% CI), p-value	Standardized Effect Size (95% CI)
Age (years)				
<65	76	31		
Day 85	6.34 (-8.41, 21.09)	-28.51 (-52.35, -4.67)	34.85 (6.81, 62.89), 0.0151	0.51 (0.08, 0.95)
Day 169	11.47 (-3.57, 26.50)	-27.86 (-52.50, -3.22)	39.33 (10.46, 68.20), 0.0079	0.53 (0.10, 0.96)
Month 9	11.02 (-6.00, 28.03)	-12.77 (-40.81, 15.26)	23.79 (-9.01, 56.58), 0.1541	0.27 (-0.16, 0.70)
Day 337	19.54 (3.72, 35.36)	-36.35 (-62.07, -10.64)	55.90 (25.71, 86.09), 0.0003	0.75 (0.31, 1.18)
Day 421	28.54 (10.10, 46.97)	-24.22 (-55.21, 6.77)	52.76 (16.70, 88.82), 0.0044	0.56 (0.12, 1.00)
Day 505	27.81 (8.73, 46.89)	-18.93 (-51.07, 13.22)	46.74 (9.35, 84.12), 0.0146	0.49 (0.05, 0.93)
Month 18	27.82 (8.16, 47.48)	-6.98 (-39.90, 25.94)	34.80 (-3.54, 73.15), 0.0749	0.33 (-0.10, 0.76)
≥65	44	10		
Day 85	-9.33 (-27.63, 8.98)	29.62 (-7.60, 66.84)	-38.95 (-80.42, 2.53), 0.0655	-0.56 (-1.24, 0.13)
Day 169	-4.20 (-22.74, 14.34)	30.27 (-7.75, 68.29)	-34.47 (-76.77, 7.83), 0.1096	-0.53 (-1.24, 0.19)
Month 9	-4.65 (-24.79, 15.48)	45.36 (5.26, 85.46)	-50.01 (-94.88, -5.14), 0.0291	-0.68 (-1.40, 0.04)
Day 337	3.87 (-15.25, 23.00)	21.77 (-16.73, 60.28)	-17.90 (-60.89, 25.09), 0.4125	-0.23 (-0.91, 0.45)
Day 421	12.87 (-8.47, 34.21)	33.91 (-8.26, 76.08)	-21.04 (-68.29, 26.22), 0.3813	-0.23 (-0.94, 0.47)
Day 505	12.14 (-9.75, 34.04)	39.20 (-3.84, 82.25)	-27.06 (-75.35, 21.23), 0.2707	-0.28 (-0.98, 0.43)
Month 18	12.15 (-10.24, 34.54)	51.15 (7.54, 94.76)	-38.99 (-88.01, 10.02), 0.1184	-0.44 (-1.16, 0.27)
p-value of Treatment*Age	0.0017			

mBMI value = albumin (g/L) x weight (kg) / height (m)^2; higher values indicate higher nutritional status. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.
LS estimates and p-value derived from mixed-effects model for repeated measures (MMRM), controlling for categorical factors (treatment, visit), the subgroup variable, continuous covariate (baseline value), and interaction (treatment by visit, treatment by subgroup).
Standardized effect size (d) = LS mean difference/estimated pooled standard deviation with the small sample bias correction.

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

Alnylam Pharmaceuticals Inc.
ALN-TTRSC02-002

Table 5.2
Modified Body Mass Index (mBMI): Change from Baseline to Month 18, MMRM Model
Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A) Subgroup Analysis
mITT Population

Subgroup Visit	LS Mean (95% CI) Vutrisiran (HELIOS-A) (N=122)	LS Mean (95% CI) Patisiran (HELIOS-A) (N=42)	LS Mean Difference (Vutrisiran-Patisiran) (95% CI), p-value	Standardized Effect Size (95% CI)
Sex				
Male	77	26		
Day 85	-0.62 (-15.68, 14.44)	-3.35 (-29.12, 22.41)	2.73 (-27.11, 32.57), 0.8570	0.04 (-0.41, 0.48)
Day 169	4.47 (-10.67, 19.60)	-2.80 (-29.14, 23.54)	7.27 (-23.11, 37.64), 0.6374	0.10 (-0.35, 0.55)
Month 9	4.02 (-13.27, 21.31)	13.03 (-17.01, 43.08)	-9.01 (-43.68, 25.65), 0.6086	-0.11 (-0.57, 0.35)
Day 337	12.52 (-3.51, 28.56)	-10.57 (-38.34, 17.19)	23.10 (-8.96, 55.15), 0.1569	0.30 (-0.16, 0.75)
Day 421	21.54 (3.12, 39.95)	1.41 (-30.96, 33.77)	20.13 (-17.10, 57.37), 0.2876	0.23 (-0.24, 0.69)
Day 505	20.77 (1.49, 40.05)	6.73 (-27.09, 40.56)	14.04 (-24.90, 52.97), 0.4779	0.14 (-0.32, 0.61)
Month 18	20.80 (1.07, 40.53)	18.62 (-15.72, 52.96)	2.18 (-37.42, 41.79), 0.9136	0.02 (-0.44, 0.49)
Female	43	15		
Day 85	2.88 (-16.08, 21.84)	-33.80 (-66.54, -1.07)	36.68 (-1.15, 74.51), 0.0573	0.59 (-0.03, 1.22)
Day 169	7.97 (-10.98, 26.92)	-33.25 (-66.12, -0.39)	41.22 (3.28, 79.16), 0.0334	0.59 (-0.03, 1.21)
Month 9	7.52 (-13.25, 28.29)	-17.42 (-52.91, 18.07)	24.94 (-16.18, 66.06), 0.2332	0.27 (-0.33, 0.88)
Day 337	16.02 (-3.70, 35.75)	-41.02 (-74.59, -7.46)	57.05 (18.11, 95.98), 0.0043	0.74 (0.14, 1.34)
Day 421	25.04 (3.31, 46.76)	-29.05 (-66.48, 8.39)	54.09 (10.80, 97.37), 0.0146	0.54 (-0.06, 1.15)
Day 505	24.27 (1.82, 46.73)	-23.72 (-62.46, 15.03)	47.99 (3.21, 92.77), 0.0358	0.48 (-0.12, 1.08)
Month 18	24.30 (1.47, 47.13)	-11.83 (-51.06, 27.39)	36.14 (-9.25, 81.52), 0.1180	0.36 (-0.22, 0.95)
p-value of Treatment*Sex	0.1214			

mBMI value = albumin (g/L) x weight (kg) / height (m)^2; higher values indicate higher nutritional status. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.
LS estimates and p-value derived from mixed-effects model for repeated measures (MMRM), controlling for categorical factors (treatment, visit), the subgroup variable, continuous covariate (baseline value), and interaction (treatment by visit, treatment by subgroup).
Standardized effect size (d) = LS mean difference/estimated pooled standard deviation with the small sample bias correction.

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Table 5.2
Modified Body Mass Index (mBMI): Change from Baseline to Month 18, MMRM Model
Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A) Subgroup Analysis
mITT Population

Subgroup Visit	LS Mean (95% CI) Vutrisiran (HELIOS-A) (N=122)	LS Mean (95% CI) Patisiran (HELIOS-A) (N=42)	LS Mean Difference (Vutrisiran-Patisiran) (95% CI), p-value	Standardized Effect Size (95% CI)
Race				
White	84	28		
Day 85	-3.52 (-18.36, 11.33)	-10.47 (-36.12, 15.18)	6.95 (-22.65, 36.56), 0.6435	0.10 (-0.34, 0.54)
Day 169	1.74 (-13.02, 16.50)	-10.41 (-36.05, 15.23)	12.15 (-17.41, 41.70), 0.4184	0.17 (-0.26, 0.60)
Month 9	1.26 (-15.49, 18.02)	5.04 (-23.88, 33.96)	-3.78 (-37.18, 29.62), 0.8236	-0.04 (-0.48, 0.39)
Day 337	9.78 (-5.71, 25.27)	-18.53 (-45.12, 8.06)	28.31 (-2.44, 59.06), 0.0709	0.37 (-0.05, 0.80)
Day 421	18.80 (0.81, 36.80)	-6.53 (-37.94, 24.88)	25.34 (-10.84, 61.51), 0.1687	0.27 (-0.17, 0.71)
Day 505	18.03 (-0.86, 36.91)	-1.16 (-34.15, 31.83)	19.19 (-18.80, 57.18), 0.3202	0.19 (-0.25, 0.63)
Month 18	18.06 (-1.24, 37.35)	10.72 (-22.73, 44.17)	7.34 (-31.25, 45.93), 0.7080	0.07 (-0.36, 0.50)
All Other Races	36	13		
Day 85	9.86 (-10.80, 30.52)	-21.51 (-55.89, 12.87)	31.37 (-8.64, 71.37), 0.1236	0.47 (-0.16, 1.10)
Day 169	15.11 (-5.65, 35.88)	-21.44 (-56.63, 13.74)	36.56 (-4.20, 77.31), 0.0784	0.51 (-0.17, 1.18)
Month 9	14.64 (-7.58, 36.85)	-6.00 (-43.44, 31.45)	20.63 (-22.80, 64.07), 0.3502	0.29 (-0.38, 0.97)
Day 337	23.16 (1.84, 44.47)	-29.56 (-65.34, 6.21)	52.72 (11.18, 94.26), 0.0131	0.67 (0.01, 1.33)
Day 421	32.18 (9.00, 55.36)	-17.57 (-57.04, 21.91)	49.75 (4.06, 95.43), 0.0330	0.56 (-0.12, 1.24)
Day 505	31.41 (7.55, 55.26)	-12.19 (-52.82, 28.43)	43.60 (-3.42, 90.62), 0.0690	0.50 (-0.17, 1.18)
Month 18	31.44 (7.27, 55.60)	-0.31 (-41.30, 40.67)	31.75 (-15.74, 79.24), 0.1891	0.39 (-0.29, 1.06)
p-value of Treatment*Race	0.2835			

mBMI value = albumin (g/L) x weight (kg) / height (m)^2; higher values indicate higher nutritional status. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.
LS estimates and p-value derived from mixed-effects model for repeated measures (MMRM), controlling for categorical factors (treatment, visit), the subgroup variable, continuous covariate (baseline value), and interaction (treatment by visit, treatment by subgroup).
Standardized effect size (d) = LS mean difference/estimated pooled standard deviation with the small sample bias correction.

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Table 5.2
Modified Body Mass Index (mBMI): Change from Baseline to Month 18, MMRM Model
Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A) Subgroup Analysis
mITT Population

Subgroup Visit	LS Mean (95% CI) Vutrisiran (HELIOS-A) (N=122)	LS Mean (95% CI) Patisiran (HELIOS-A) (N=42)	LS Mean Difference (Vutrisiran-Patisiran) (95% CI), p-value	Standardized Effect Size (95% CI)
Region				
North America	27	8		
Day 85	15.08 (-9.29, 39.45)	-5.28 (-48.96, 38.40)	20.36 (-28.72, 69.44), 0.4141	0.25 (-0.57, 1.07)
Day 169	20.20 (-4.06, 44.46)	-4.66 (-48.12, 38.79)	24.87 (-23.96, 73.70), 0.3162	0.30 (-0.47, 1.08)
Month 9	19.68 (-5.61, 44.97)	10.34 (-34.82, 55.50)	9.34 (-41.52, 60.19), 0.7177	0.11 (-0.71, 0.93)
Day 337	28.24 (3.51, 52.98)	-12.96 (-57.01, 31.09)	41.20 (-8.39, 90.80), 0.1029	0.51 (-0.28, 1.30)
Day 421	37.21 (10.92, 63.51)	-0.92 (-48.04, 46.20)	38.13 (-14.97, 91.23), 0.1584	0.41 (-0.41, 1.22)
Day 505	36.47 (9.66, 63.28)	4.34 (-43.62, 52.29)	32.14 (-21.96, 86.24), 0.2430	0.34 (-0.53, 1.21)
Month 18	36.51 (9.43, 63.59)	16.19 (-32.09, 64.47)	20.32 (-34.20, 74.84), 0.4634	0.22 (-0.60, 1.04)
Western Europe	40	19		
Day 85	-2.39 (-22.06, 17.28)	-8.30 (-37.72, 21.12)	5.91 (-29.51, 41.32), 0.7424	0.08 (-0.46, 0.62)
Day 169	2.73 (-17.00, 22.46)	-7.68 (-38.02, 22.66)	10.41 (-25.79, 46.62), 0.5712	0.15 (-0.43, 0.72)
Month 9	2.21 (-18.75, 23.16)	7.32 (-25.04, 39.68)	-5.12 (-43.69, 33.45), 0.7938	-0.06 (-0.61, 0.49)
Day 337	10.77 (-9.44, 30.98)	-15.98 (-46.85, 14.90)	26.75 (-10.17, 63.67), 0.1547	0.34 (-0.21, 0.89)
Day 421	19.74 (-2.47, 41.95)	-3.94 (-39.05, 31.17)	23.68 (-17.89, 65.24), 0.2627	0.28 (-0.27, 0.83)
Day 505	19.00 (-3.85, 41.84)	1.32 (-35.03, 37.66)	17.68 (-25.26, 60.63), 0.4179	0.19 (-0.36, 0.74)
Month 18	19.04 (-4.11, 42.19)	13.17 (-23.50, 49.85)	5.87 (-37.52, 49.25), 0.7901	0.06 (-0.49, 0.61)

mBMI value = albumin (g/L) x weight (kg) / height (m)^2; higher values indicate higher nutritional status. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.
LS estimates and p-value derived from mixed-effects model for repeated measures (MMRM), controlling for categorical factors (treatment, visit), the subgroup variable, continuous covariate (baseline value), and interaction (treatment by visit, treatment by subgroup).
Standardized effect size (d) = LS mean difference/estimated pooled standard deviation with the small sample bias correction.

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Table 5.2
Modified Body Mass Index (mBMI): Change from Baseline to Month 18, MMRM Model
Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A) Subgroup Analysis
mITT Population

Subgroup Visit	LS Mean (95% CI) Vutrisiran (HELIOS-A) (N=122)	LS Mean (95% CI) Patisiran (HELIOS-A) (N=42)	LS Mean Difference (Vutrisiran-Patisiran) (95% CI), p-value	Standardized Effect Size (95% CI)
Rest of World	53	14		
Day 85	-4.39 (-22.20, 13.41)	-27.16 (-60.85, 6.52)	22.77 (-15.10, 60.65), 0.2371	0.37 (-0.24, 0.97)
Day 169	0.73 (-17.12, 18.58)	-26.55 (-60.14, 7.05)	27.28 (-10.54, 65.09), 0.1563	0.39 (-0.19, 0.98)
Month 9	0.20 (-19.06, 19.47)	-11.54 (-47.33, 24.24)	11.75 (-28.68, 52.17), 0.5673	0.15 (-0.45, 0.75)
Day 337	8.77 (-9.69, 27.23)	-34.84 (-69.23, -0.45)	43.61 (4.81, 82.42), 0.0278	0.59 (-0.00, 1.18)
Day 421	17.74 (-2.89, 38.37)	-22.80 (-61.08, 15.48)	40.54 (-2.74, 83.82), 0.0662	0.41 (-0.22, 1.03)
Day 505	17.00 (-4.31, 38.31)	-17.55 (-56.93, 21.84)	34.55 (-10.04, 79.13), 0.1282	0.35 (-0.26, 0.95)
Month 18	17.04 (-4.59, 38.67)	-5.69 (-45.39, 34.01)	22.73 (-22.29, 67.75), 0.3208	0.23 (-0.37, 0.83)
p-value of Treatment*Region	0.7549			

mBMI value = albumin (g/L) x weight (kg) / height (m)^2; higher values indicate higher nutritional status. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.
LS estimates and p-value derived from mixed-effects model for repeated measures (MMRM), controlling for categorical factors (treatment, visit), the subgroup variable, continuous covariate (baseline value), and interaction (treatment by visit, treatment by subgroup).
Standardized effect size (d) = LS mean difference/estimated pooled standard deviation with the small sample bias correction.

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Table 5.2
Modified Body Mass Index (mBMI): Change from Baseline to Month 18, MMRM Model
Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A) Subgroup Analysis
mITT Population

Subgroup Visit	LS Mean (95% CI) Vutrisiran (HELIOS-A) (N=122)	LS Mean (95% CI) Patisiran (HELIOS-A) (N=42)	LS Mean Difference (Vutrisiran-Patisiran) (95% CI), p-value	Standardized Effect Size (95% CI)
Baseline NIS				
<50	78	27		
Day 85	5.60 (-9.40, 20.60)	-20.74 (-46.25, 4.77)	26.34 (-3.21, 55.90), 0.0803	0.36 (-0.08, 0.81)
Day 169	10.83 (-4.41, 26.06)	-20.12 (-45.98, 5.74)	30.95 (0.98, 60.93), 0.0431	0.43 (-0.01, 0.87)
Month 9	10.33 (-6.94, 27.60)	-4.99 (-34.41, 24.43)	15.32 (-18.77, 49.40), 0.3763	0.19 (-0.26, 0.64)
Day 337	18.85 (2.81, 34.89)	-28.54 (-55.63, -1.44)	47.38 (15.93, 78.83), 0.0034	0.66 (0.22, 1.11)
Day 421	27.86 (9.37, 46.36)	-16.53 (-48.41, 15.36)	44.39 (7.56, 81.22), 0.0184	0.53 (0.07, 0.98)
Day 505	27.05 (7.66, 46.45)	-11.22 (-44.75, 22.31)	38.27 (-0.43, 76.98), 0.0526	0.42 (-0.03, 0.87)
Month 18	27.11 (7.38, 46.85)	0.65 (-33.23, 34.53)	26.47 (-12.72, 65.65), 0.1843	0.27 (-0.18, 0.71)
≥50	42	14		
Day 85	-8.82 (-28.25, 10.60)	-0.78 (-34.14, 32.58)	-8.05 (-46.54, 30.45), 0.6805	-0.13 (-0.75, 0.49)
Day 169	-3.60 (-23.05, 15.86)	-0.16 (-34.48, 34.16)	-3.44 (-42.79, 35.91), 0.8634	-0.05 (-0.70, 0.61)
Month 9	-4.10 (-25.20, 17.00)	14.98 (-21.61, 51.56)	-19.07 (-61.21, 23.06), 0.3732	-0.20 (-0.82, 0.42)
Day 337	4.42 (-15.67, 24.51)	-8.57 (-43.40, 26.26)	12.99 (-27.12, 53.10), 0.5237	0.15 (-0.47, 0.76)
Day 421	13.44 (-8.64, 35.51)	3.44 (-35.22, 42.09)	10.00 (-34.42, 54.43), 0.6577	0.09 (-0.54, 0.72)
Day 505	12.63 (-10.24, 35.49)	8.75 (-31.16, 48.65)	3.88 (-42.02, 49.79), 0.8678	0.03 (-0.60, 0.67)
Month 18	12.69 (-10.46, 35.83)	20.61 (-19.58, 60.81)	-7.93 (-54.22, 38.37), 0.7362	-0.08 (-0.71, 0.56)
p-value of Treatment*Baseline NIS	0.1224			

mBMI value = albumin (g/L) x weight (kg) / height (m)^2; higher values indicate higher nutritional status. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.
LS estimates and p-value derived from mixed-effects model for repeated measures (MMRM), controlling for categorical factors (treatment, visit), the subgroup variable, continuous covariate (baseline value), and interaction (treatment by visit, treatment by subgroup).
Standardized effect size (d) = LS mean difference/estimated pooled standard deviation with the small sample bias correction.

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Table 5.2
Modified Body Mass Index (mBMI): Change from Baseline to Month 18, MMRM Model
Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A) Subgroup Analysis
mITT Population

Subgroup Visit	LS Mean (95% CI) Vutrisiran (HELIOS-A) (N=122)	LS Mean (95% CI) Patisiran (HELIOS-A) (N=42)	LS Mean Difference (Vutrisiran-Patisiran) (95% CI), p-value	Standardized Effect Size (95% CI)
Previous Tetramer Stabilizer Use				
Yes	74	33		
Day 85	-2.62 (-18.06, 12.82)	-16.63 (-40.63, 7.38)	14.00 (-14.50, 42.51), 0.3335	0.19 (-0.23, 0.60)
Day 169	2.53 (-12.85, 17.90)	-16.47 (-40.94, 8.01)	19.00 (-9.87, 47.86), 0.1958	0.26 (-0.16, 0.68)
Month 9	2.05 (-15.20, 19.30)	-1.15 (-28.86, 26.56)	3.20 (-29.41, 35.81), 0.8465	0.04 (-0.37, 0.45)
Day 337	10.59 (-5.68, 26.85)	-24.58 (-50.34, 1.18)	35.17 (4.74, 65.60), 0.0238	0.47 (0.05, 0.89)
Day 421	19.61 (1.07, 38.16)	-12.62 (-43.09, 17.86)	32.23 (-3.41, 67.88), 0.0761	0.38 (-0.04, 0.80)
Day 505	18.83 (-0.64, 38.30)	-7.26 (-39.44, 24.93)	26.08 (-11.50, 63.67), 0.1725	0.27 (-0.15, 0.70)
Month 18	18.87 (-0.95, 38.69)	4.62 (-27.95, 37.20)	14.25 (-23.85, 52.35), 0.4615	0.14 (-0.28, 0.56)
No	46	8		
Day 85	5.73 (-12.90, 24.37)	-2.96 (-46.21, 40.28)	8.70 (-38.23, 55.62), 0.7151	0.14 (-0.65, 0.92)
Day 169	10.88 (-7.70, 29.47)	-2.80 (-45.73, 40.12)	13.69 (-32.93, 60.30), 0.5631	0.20 (-0.54, 0.94)
Month 9	10.41 (-9.78, 30.59)	12.51 (-32.49, 57.51)	-2.10 (-51.27, 47.06), 0.9328	-0.03 (-0.87, 0.82)
Day 337	18.94 (-0.45, 38.33)	-10.92 (-54.72, 32.88)	29.86 (-17.88, 77.60), 0.2189	0.36 (-0.38, 1.11)
Day 421	27.97 (6.66, 49.28)	1.04 (-45.77, 47.86)	26.92 (-24.36, 78.21), 0.3020	0.25 (-0.59, 1.10)
Day 505	27.19 (5.09, 49.28)	6.41 (-41.40, 54.22)	20.78 (-31.74, 73.30), 0.4365	0.20 (-0.58, 0.99)
Month 18	27.23 (4.83, 49.63)	18.29 (-29.78, 66.36)	8.94 (-43.95, 61.83), 0.7394	0.10 (-0.69, 0.88)
p-value of Treatment*Previous Tetramer Stabilizer Use	0.8349			

mBMI value = albumin (g/L) x weight (kg) / height (m)^2; higher values indicate higher nutritional status. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.
LS estimates and p-value derived from mixed-effects model for repeated measures (MMRM), controlling for categorical factors (treatment, visit), the subgroup variable, continuous covariate (baseline value), and interaction (treatment by visit, treatment by subgroup).
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Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A) Subgroup Analysis
mITT Population

Subgroup Visit	LS Mean (95% CI) Vutrisiran (HELIOS-A) (N=122)	LS Mean (95% CI) Patisiran (HELIOS-A) (N=42)	LS Mean Difference (Vutrisiran-Patisiran) (95% CI), p-value	Standardized Effect Size (95% CI)
Genotype				
V30M	53	20		
Day 85	1.30 (-16.17, 18.78)	-9.60 (-38.55, 19.35)	10.91 (-22.83, 44.64), 0.5243	0.16 (-0.36, 0.68)
Day 169	6.47 (-11.14, 24.08)	-9.27 (-38.76, 20.22)	15.74 (-18.53, 50.01), 0.3661	0.22 (-0.31, 0.75)
Month 9	5.98 (-13.32, 25.27)	6.01 (-26.09, 38.12)	-0.04 (-37.42, 37.35), 0.9985	-0.00 (-0.52, 0.52)
Day 337	14.48 (-3.80, 32.76)	-17.51 (-47.64, 12.62)	32.00 (-3.17, 67.16), 0.0743	0.48 (-0.04, 0.99)
Day 421	23.51 (3.09, 43.93)	-5.51 (-39.95, 28.94)	29.01 (-10.97, 69.00), 0.1540	0.39 (-0.13, 0.91)
Day 505	22.76 (1.59, 43.93)	-0.14 (-35.99, 35.70)	22.90 (-18.67, 64.47), 0.2786	0.26 (-0.25, 0.77)
Month 18	22.79 (1.23, 44.34)	11.73 (-24.56, 48.02)	11.06 (-31.09, 53.20), 0.6055	0.13 (-0.38, 0.64)
non-V30M	67	21		
Day 85	-0.01 (-16.06, 16.03)	-18.27 (-46.65, 10.10)	18.26 (-14.27, 50.79), 0.2695	0.25 (-0.25, 0.75)
Day 169	5.15 (-10.98, 21.29)	-17.94 (-46.80, 10.92)	23.09 (-9.91, 56.09), 0.1690	0.31 (-0.18, 0.81)
Month 9	4.66 (-13.27, 22.59)	-2.66 (-34.49, 29.18)	7.32 (-29.16, 43.79), 0.6928	0.09 (-0.42, 0.60)
Day 337	13.17 (-3.65, 29.99)	-26.18 (-56.08, 3.71)	39.35 (5.11, 73.59), 0.0245	0.46 (-0.04, 0.97)
Day 421	22.19 (3.03, 41.36)	-14.18 (-48.45, 20.10)	36.37 (-2.84, 75.58), 0.0689	0.34 (-0.18, 0.86)
Day 505	21.44 (1.52, 41.37)	-8.81 (-44.31, 26.68)	30.26 (-10.40, 70.91), 0.1438	0.29 (-0.24, 0.82)
Month 18	21.47 (1.13, 41.82)	3.06 (-32.94, 39.06)	18.41 (-22.88, 59.71), 0.3804	0.17 (-0.35, 0.69)
p-value of Treatment*Genotype	0.7277			

mBMI value = albumin (g/L) x weight (kg) / height (m)^2; higher values indicate higher nutritional status. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.
LS estimates and p-value derived from mixed-effects model for repeated measures (MMRM), controlling for categorical factors (treatment, visit), the subgroup variable, continuous covariate (baseline value), and interaction (treatment by visit, treatment by subgroup).
Standardized effect size (d) = LS mean difference/estimated pooled standard deviation with the small sample bias correction.

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Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A) Subgroup Analysis
mITT Population

Subgroup Visit	LS Mean (95% CI) Vutrisiran (HELIOS-A) (N=122)	LS Mean (95% CI) Patisiran (HELIOS-A) (N=42)	LS Mean Difference (Vutrisiran-Patisiran) (95% CI), p-value	Standardized Effect Size (95% CI)
FAP Stage				
I	84	30		
Day 85	2.36 (-12.12, 16.85)	-30.48 (-55.17, -5.78)	32.84 (4.22, 61.46), 0.0248	0.47 (0.04, 0.90)
Day 169	7.46 (-6.93, 21.85)	-28.30 (-52.62, -3.99)	35.77 (7.52, 64.01), 0.0134	0.50 (0.08, 0.92)
Month 9	7.02 (-9.69, 23.73)	-13.83 (-42.21, 14.54)	20.85 (-12.07, 53.77), 0.2129	0.24 (-0.18, 0.67)
Day 337	15.55 (0.13, 30.97)	-37.28 (-63.18, -11.38)	52.82 (22.69, 82.96), 0.0007	0.71 (0.29, 1.14)
Day 421	24.54 (6.57, 42.51)	-25.14 (-56.05, 5.78)	49.68 (13.93, 85.43), 0.0067	0.56 (0.13, 0.98)
Day 505	23.77 (4.90, 42.64)	-20.21 (-52.79, 12.37)	43.98 (6.34, 81.62), 0.0223	0.47 (0.05, 0.90)
Month 18	23.82 (4.55, 43.08)	-8.25 (-41.26, 24.77)	32.06 (-6.15, 70.28), 0.0995	0.32 (-0.10, 0.74)
II&III	36	11		
Day 85	-3.50 (-23.87, 16.87)	29.18 (-7.32, 65.68)	-32.68 (-74.43, 9.08), 0.1243	-0.46 (-1.13, 0.22)
Day 169	1.60 (-18.60, 21.81)	31.35 (-6.19, 68.90)	-29.75 (-72.35, 12.84), 0.1700	-0.43 (-1.19, 0.33)
Month 9	1.16 (-20.69, 23.01)	45.83 (6.21, 85.44)	-44.67 (-89.87, 0.54), 0.0528	-0.57 (-1.30, 0.17)
Day 337	9.69 (-11.16, 30.54)	22.38 (-15.64, 60.40)	-12.69 (-56.01, 30.62), 0.5641	-0.15 (-0.84, 0.53)
Day 421	18.68 (-4.14, 41.51)	34.52 (-7.11, 76.15)	-15.84 (-63.28, 31.60), 0.5113	-0.16 (-0.91, 0.60)
Day 505	17.92 (-5.61, 41.44)	39.45 (-3.15, 82.05)	-21.54 (-70.16, 27.09), 0.3839	-0.20 (-0.95, 0.56)
Month 18	17.96 (-5.88, 41.80)	51.41 (8.45, 94.38)	-33.45 (-82.55, 15.65), 0.1808	-0.33 (-1.09, 0.43)
p-value of Treatment*FAP Stage	0.0054			

mBMI value = albumin (g/L) x weight (kg) / height (m)^2; higher values indicate higher nutritional status. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.
LS estimates and p-value derived from mixed-effects model for repeated measures (MMRM), controlling for categorical factors (treatment, visit), the subgroup variable, continuous covariate (baseline value), and interaction (treatment by visit, treatment by subgroup).
Standardized effect size (d) = LS mean difference/estimated pooled standard deviation with the small sample bias correction.

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Table 5.2
Modified Body Mass Index (mBMI): Change from Baseline to Month 18, MMRM Model
Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A) Subgroup Analysis
mITT Population

Subgroup Visit	LS Mean (95% CI) Vutrisiran (HELIOS-A) (N=122)	LS Mean (95% CI) Patisiran (HELIOS-A) (N=42)	LS Mean Difference (Vutrisiran-Patisiran) (95% CI), p-value	Standardized Effect Size (95% CI)
Cardiac Subpopulation				
Yes	39	14		
Day 85	-20.94 (-40.42, -1.47)	-3.89 (-36.59, 28.82)	-17.06 (-55.04, 20.92), 0.3767	-0.25 (-0.88, 0.37)
Day 169	-15.66 (-35.24, 3.92)	-3.75 (-36.84, 29.35)	-11.92 (-50.30, 26.46), 0.5410	-0.17 (-0.79, 0.44)
Month 9	-16.21 (-37.38, 4.96)	11.68 (-23.93, 47.28)	-27.89 (-69.23, 13.46), 0.1851	-0.32 (-0.94, 0.31)
Day 337	-7.71 (-27.86, 12.44)	-11.95 (-45.63, 21.73)	4.24 (-34.94, 43.41), 0.8313	0.05 (-0.55, 0.65)
Day 421	1.26 (-21.02, 23.54)	0.22 (-37.62, 38.05)	1.04 (-42.79, 44.88), 0.9626	0.01 (-0.61, 0.63)
Day 505	0.60 (-22.04, 23.25)	5.38 (-33.16, 43.91)	-4.77 (-49.40, 39.85), 0.8332	-0.04 (-0.67, 0.58)
Month 18	0.59 (-22.57, 23.74)	17.28 (-21.95, 56.51)	-16.69 (-62.18, 28.79), 0.4704	-0.17 (-0.80, 0.45)
No	81	27		
Day 85	10.86 (-3.69, 25.40)	-19.25 (-44.34, 5.85)	30.10 (1.13, 59.08), 0.0418	0.43 (-0.01, 0.88)
Day 169	16.14 (1.36, 30.92)	-19.11 (-45.02, 6.81)	35.25 (5.44, 65.05), 0.0207	0.48 (0.03, 0.93)
Month 9	15.59 (-1.18, 32.37)	-3.68 (-32.85, 25.49)	19.28 (-14.35, 52.90), 0.2595	0.24 (-0.21, 0.69)
Day 337	24.09 (8.62, 39.56)	-27.31 (-54.12, -0.50)	51.40 (20.47, 82.33), 0.0012	0.72 (0.27, 1.17)
Day 421	33.06 (14.92, 51.20)	-15.14 (-47.05, 16.77)	48.21 (11.52, 84.89), 0.0103	0.57 (0.11, 1.03)
Day 505	32.41 (13.80, 51.01)	-9.98 (-42.67, 22.70)	42.39 (4.80, 79.98), 0.0273	0.48 (0.03, 0.94)
Month 18	32.39 (13.16, 51.62)	1.92 (-31.59, 35.43)	30.47 (-8.15, 69.08), 0.1213	0.30 (-0.15, 0.75)
p-value of Treatment*Cardiac Subpopulation	0.0308			

mBMI value = albumin (g/L) x weight (kg) / height (m)^2; higher values indicate higher nutritional status. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.
LS estimates and p-value derived from mixed-effects model for repeated measures (MMRM), controlling for categorical factors (treatment, visit), the subgroup variable, continuous covariate (baseline value), and interaction (treatment by visit, treatment by subgroup).
Standardized effect size (d) = LS mean difference/estimated pooled standard deviation with the small sample bias correction.

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Table 5.2
Modified Body Mass Index (mBMI): Change from Baseline to Month 18, MMRM Model
Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A) Subgroup Analysis
mITT Population

Subgroup Visit	LS Mean (95% CI) Vutrisiran (HELIOS-A) (N=122)	LS Mean (95% CI) Patisiran (HELIOS-A) (N=42)	LS Mean Difference (Vutrisiran-Patisiran) (95% CI), p-value	Standardized Effect Size (95% CI)
Weight (kg)				
<65	45	15		
Day 85	-12.26 (-33.07, 8.54)	-52.18 (-85.68, -18.68)	39.91 (3.04, 76.78), 0.0340	0.79 (0.16, 1.42)
Day 169	-7.17 (-28.13, 13.80)	-51.30 (-84.99, -17.61)	44.14 (6.94, 81.33), 0.0203	0.68 (0.06, 1.31)
Month 9	-7.67 (-29.91, 14.58)	-35.65 (-71.26, -0.05)	27.98 (-11.67, 67.64), 0.1656	0.34 (-0.25, 0.94)
Day 337	0.88 (-20.71, 22.48)	-58.94 (-93.20, -24.67)	59.82 (21.74, 97.90), 0.0022	0.82 (0.22, 1.41)
Day 421	9.89 (-13.56, 33.34)	-46.91 (-85.02, -8.79)	56.79 (14.22, 99.37), 0.0092	0.65 (0.05, 1.26)
Day 505	9.11 (-15.00, 33.23)	-41.64 (-81.03, -2.26)	50.76 (6.68, 94.83), 0.0242	0.57 (-0.03, 1.18)
Month 18	9.17 (-15.20, 33.54)	-29.79 (-69.45, 9.86)	38.96 (-5.50, 83.42), 0.0856	0.47 (-0.12, 1.05)
≥65	75	26		
Day 85	8.49 (-7.75, 24.74)	6.63 (-19.15, 32.42)	1.86 (-27.54, 31.25), 0.9008	0.02 (-0.42, 0.47)
Day 169	13.59 (-2.76, 29.94)	7.51 (-19.11, 34.12)	6.08 (-24.05, 36.21), 0.6909	0.08 (-0.37, 0.53)
Month 9	13.09 (-4.84, 31.02)	23.16 (-6.33, 52.64)	-10.07 (-43.58, 23.44), 0.5540	-0.12 (-0.58, 0.34)
Day 337	21.64 (4.52, 38.76)	-0.13 (-28.00, 27.75)	21.76 (-9.89, 53.42), 0.1767	0.28 (-0.18, 0.73)
Day 421	30.64 (11.25, 50.03)	11.90 (-20.60, 44.41)	18.74 (-18.21, 55.68), 0.3184	0.20 (-0.27, 0.66)
Day 505	29.87 (9.67, 50.07)	17.17 (-16.78, 51.11)	12.70 (-25.94, 51.34), 0.5175	0.12 (-0.34, 0.59)
Month 18	29.92 (9.42, 50.42)	29.02 (-5.22, 63.26)	0.90 (-38.15, 39.96), 0.9636	0.01 (-0.46, 0.47)
p-value of Treatment*Weight	0.0756			

mBMI value = albumin (g/L) x weight (kg) / height (m)^2; higher values indicate higher nutritional status. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.
LS estimates and p-value derived from mixed-effects model for repeated measures (MMRM), controlling for categorical factors (treatment, visit), the subgroup variable, continuous covariate (baseline value), and interaction (treatment by visit, treatment by subgroup).
Standardized effect size (d) = LS mean difference/estimated pooled standard deviation with the small sample bias correction.

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Table 5.3
Modified Body Mass Index (mBMI): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Age (years): <65

Subgroup Visit	Vutrisiran (HELIOS-A) (N=76)	Patisiran (HELIOS-A) (N=31)
Baseline		
n	76	31
Mean (SD)	1059.3 (246.4)	1040.3 (229.4)
SE	28.3	41.2
Median	1019.5	1027.6
Min, Max	589, 1723	646, 1636
Day 85		
Actual Value		
n	73	29
Mean (SD)	1067.6 (229.9)	1009.7 (219.2)
SE	26.9	40.7
Median	1024.9	1029.4
Min, Max	667, 1750	590, 1569
Change from baseline		
n	73	29
Mean (SD)	6.1 (74.0)	-29.9 (71.4)
SE	8.7	13.3
Median	10.1	-35.6
Min, Max	-295, 180	-183, 108

mBMI value = albumin (g/L) x weight (kg) / height (m)^2; higher values indicate higher nutritional status. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 5.3
Modified Body Mass Index (mBMI): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Age (years): <65

Subgroup Visit	Vutrisiran (HELIOS-A) (N=76)	Patisiran (HELIOS-A) (N=31)
Day 169		
Actual Value		
n	75	29
Mean (SD)	1067.5 (238.6)	1021.5 (227.1)
SE	27.6	42.2
Median	1030.4	1019.4
Min, Max	599, 1778	583, 1578
Change from baseline		
n	75	29
Mean (SD)	12.2 (77.8)	-23.1 (74.7)
SE	9.0	13.9
Median	11.0	-36.4
Min, Max	-175, 221	-168, 129

mBMI value = albumin (g/L) x weight (kg) / height (m)^2; higher values indicate higher nutritional status. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 5.3
Modified Body Mass Index (mBMI): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Age (years): <65

Subgroup Visit	Vutrisiran (HELIOS-A) (N=76)	Patisiran (HELIOS-A) (N=31)
Month 9		
Actual Value		
n	73	29
Mean (SD)	1067.0 (243.0)	1031.2 (267.2)
SE	28.4	49.6
Median	1028.5	1001.9
Min, Max	587, 1747	584, 1634
Change from baseline		
n	73	29
Mean (SD)	3.7 (75.7)	-18.6 (109.3)
SE	8.9	20.3
Median	14.9	-14.2
Min, Max	-218, 145	-369, 169

mBMI value = albumin (g/L) x weight (kg) / height (m)^2; higher values indicate higher nutritional status. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 5.3
Modified Body Mass Index (mBMI): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Age (years): <65

Subgroup Visit	Vutrisiran (HELIOS-A) (N=76)	Patisiran (HELIOS-A) (N=31)
Day 337		
Actual Value		
n	73	30
Mean (SD)	1076.6 (235.4)	1003.0 (231.3)
SE	27.5	42.2
Median	1032.2	980.4
Min, Max	669, 1812	601, 1584
Change from baseline		
n	73	30
Mean (SD)	15.7 (71.7)	-37.6 (90.0)
SE	8.4	16.4
Median	14.8	-46.9
Min, Max	-153, 182	-317, 123

mBMI value = albumin (g/L) x weight (kg) / height (m)^2; higher values indicate higher nutritional status. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 5.3
Modified Body Mass Index (mBMI): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Age (years): <65

Subgroup Visit	Vutrisiran (HELIOS-A) (N=76)	Patisiran (HELIOS-A) (N=31)
Day 421		
Actual Value		
n	75	28
Mean (SD)	1097.9 (247.5)	1032.4 (248.8)
SE	28.6	47.0
Median	1080.1	1002.0
Min, Max	660, 1877	635, 1557
Change from baseline		
n	75	28
Mean (SD)	33.7 (90.5)	-17.2 (102.6)
SE	10.4	19.4
Median	36.6	-10.6
Min, Max	-166, 228	-388, 160

mBMI value = albumin (g/L) x weight (kg) / height (m)^2; higher values indicate higher nutritional status. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 5.3
Modified Body Mass Index (mBMI): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Age (years): <65

Subgroup Visit	Vutrisiran (HELIOS-A) (N=76)	Patisiran (HELIOS-A) (N=31)
Day 505		
Actual Value		
n	74	28
Mean (SD)	1097.5 (248.6)	1024.6 (236.3)
SE	28.9	44.7
Median	1067.4	981.7
Min, Max	598, 1858	662, 1558
Change from baseline		
n	74	28
Mean (SD)	32.2 (98.7)	-21.4 (90.9)
SE	11.5	17.2
Median	37.7	-33.9
Min, Max	-236, 249	-290, 180

mBMI value = albumin (g/L) x weight (kg) / height (m)^2; higher values indicate higher nutritional status. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 5.3
Modified Body Mass Index (mBMI): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Age (years): <65

Subgroup Visit	Vutrisiran (HELIOS-A) (N=76)	Patisiran (HELIOS-A) (N=31)
Month 18		
Actual Value		
n	74	29
Mean (SD)	1094.8 (257.8)	1037.2 (244.4)
SE	30.0	45.4
Median	1046.1	1005.6
Min, Max	572, 2120	652, 1593
Change from baseline		
n	74	29
Mean (SD)	25.9 (107.6)	-2.9 (97.2)
SE	12.5	18.0
Median	25.5	-17.6
Min, Max	-216, 397	-284, 179

mBMI value = albumin (g/L) x weight (kg) / height (m)^2; higher values indicate higher nutritional status. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 5.3
Modified Body Mass Index (mBMI): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Age (years): ≥65

Subgroup Visit	Vutrisiran (HELIOS-A) (N=46)	Patisiran (HELIOS-A) (N=11)
Baseline		
n	46	11
Mean (SD)	1054.2 (214.0)	1108.3 (230.1)
SE	31.6	69.4
Median	1060.0	1053.1
Min, Max	701, 1505	795, 1534
Day 85		
Actual Value		
n	42	10
Mean (SD)	1048.2 (210.4)	1141.0 (240.4)
SE	32.5	76.0
Median	1026.5	1054.4
Min, Max	742, 1606	825, 1570
Change from baseline		
n	42	10
Mean (SD)	-10.1 (77.1)	35.7 (35.9)
SE	11.9	11.4
Median	-5.7	35.8
Min, Max	-164, 144	-29, 83

mBMI value = albumin (g/L) x weight (kg) / height (m)^2; higher values indicate higher nutritional status. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 5.3
Modified Body Mass Index (mBMI): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Age (years): ≥65

Subgroup Visit	Vutrisiran (HELIOS-A) (N=46)	Patisiran (HELIOS-A) (N=11)
Day 169		
Actual Value		
n	43	9
Mean (SD)	1053.5 (218.2)	1142.1 (215.3)
SE	33.3	71.8
Median	1041.3	1081.2
Min, Max	645, 1559	880, 1484
Change from baseline		
n	43	9
Mean (SD)	-7.0 (63.6)	10.2 (71.3)
SE	9.7	23.8
Median	0.0	17.7
Min, Max	-154, 186	-101, 132

mBMI value = albumin (g/L) x weight (kg) / height (m)^2; higher values indicate higher nutritional status. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 5.3
Modified Body Mass Index (mBMI): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Age (years): ≥65

Subgroup Visit	Vutrisiran (HELIOS-A) (N=46)	Patisiran (HELIOS-A) (N=11)
Month 9		
Actual Value		
n	41	9
Mean (SD)	1055.4 (225.0)	1181.9 (233.8)
SE	35.1	77.9
Median	1062.5	1067.1
Min, Max	599, 1576	912, 1633
Change from baseline		
n	41	9
Mean (SD)	1.2 (72.5)	42.1 (67.2)
SE	11.3	22.4
Median	-18.3	47.0
Min, Max	-132, 198	-45, 118

mBMI value = albumin (g/L) x weight (kg) / height (m)^2; higher values indicate higher nutritional status. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 5.3
Modified Body Mass Index (mBMI): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Age (years): ≥65

Subgroup Visit	Vutrisiran (HELIOS-A) (N=46)	Patisiran (HELIOS-A) (N=11)
Day 337		
Actual Value		
n	43	10
Mean (SD)	1066.0 (219.3)	1126.3 (192.9)
SE	33.4	61.0
Median	1073.9	1090.8
Min, Max	688, 1552	880, 1547
Change from baseline		
n	43	10
Mean (SD)	6.9 (78.6)	21.0 (88.7)
SE	12.0	28.0
Median	5.4	36.3
Min, Max	-162, 190	-187, 131

mBMI value = albumin (g/L) x weight (kg) / height (m)^2; higher values indicate higher nutritional status. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 5.3
Modified Body Mass Index (mBMI): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Age (years): ≥65

Subgroup Visit	Vutrisiran (HELIOS-A) (N=46)	Patisiran (HELIOS-A) (N=11)
Day 421		
Actual Value		
n	43	9
Mean (SD)	1063.2 (238.3)	1077.9 (231.1)
SE	36.3	77.0
Median	1041.1	1049.1
Min, Max	662, 1645	780, 1553
Change from baseline		
n	43	9
Mean (SD)	2.6 (90.7)	8.8 (45.4)
SE	13.8	15.1
Median	-8.8	16.6
Min, Max	-145, 190	-57, 93

mBMI value = albumin (g/L) x weight (kg) / height (m)^2; higher values indicate higher nutritional status. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 5.3
Modified Body Mass Index (mBMI): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Age (years): ≥65

Subgroup Visit	Vutrisiran (HELIOS-A) (N=46)	Patisiran (HELIOS-A) (N=11)
Day 505		
Actual Value		
n	43	9
Mean (SD)	1064.9 (229.2)	1119.8 (257.7)
SE	34.9	85.9
Median	1039.1	1099.1
Min, Max	614, 1585	794, 1607
Change from baseline		
n	43	9
Mean (SD)	9.4 (94.6)	50.7 (104.2)
SE	14.4	34.7
Median	-4.2	63.5
Min, Max	-222, 307	-138, 187

mBMI value = albumin (g/L) x weight (kg) / height (m)^2; higher values indicate higher nutritional status. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 5.3
Modified Body Mass Index (mBMI): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Age (years): ≥65

Subgroup Visit	Vutrisiran (HELIOS-A) (N=46)	Patisiran (HELIOS-A) (N=11)
Month 18		
Actual Value		
n	41	9
Mean (SD)	1067.9 (214.9)	1107.7 (216.5)
SE	33.6	72.2
Median	1058.5	1074.4
Min, Max	710, 1552	864, 1579
Change from baseline		
n	41	9
Mean (SD)	17.7 (91.4)	38.6 (66.8)
SE	14.3	22.3
Median	19.9	45.6
Min, Max	-187, 203	-91, 124

mBMI value = albumin (g/L) x weight (kg) / height (m)^2; higher values indicate higher nutritional status. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

Alnylam Pharmaceuticals Inc.
ALN-TTRSC02-002

Table 5.3
Modified Body Mass Index (mBMI): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Sex: Male

Subgroup Visit	Vutrisiran (HELIOS-A) (N=79)	Patisiran (HELIOS-A) (N=27)
Baseline		
n	79	27
Mean (SD)	1056.9 (216.0)	1076.2 (196.9)
SE	24.3	37.9
Median	1061.2	1044.3
Min, Max	634, 1723	658, 1636
Day 85		
Actual Value		
n	74	26
Mean (SD)	1060.6 (203.2)	1068.5 (196.6)
SE	23.6	38.6
Median	1025.5	1041.7
Min, Max	669, 1750	714, 1569
Change from baseline		
n	74	26
Mean (SD)	-0.6 (81.1)	-5.3 (68.7)
SE	9.4	13.5
Median	3.0	-4.2
Min, Max	-295, 180	-153, 108

mBMI value = albumin (g/L) x weight (kg) / height (m)^2; higher values indicate higher nutritional status. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Alnylam Pharmaceuticals Inc.
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Table 5.3
Modified Body Mass Index (mBMI): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Sex: Male

Subgroup Visit	Vutrisiran (HELIOS-A) (N=79)	Patisiran (HELIOS-A) (N=27)
Day 169		
Actual Value		
n	75	25
Mean (SD)	1058.4 (217.2)	1072.3 (187.5)
SE	25.1	37.5
Median	1041.1	1066.8
Min, Max	615, 1778	769, 1578
Change from baseline		
n	75	25
Mean (SD)	1.8 (73.9)	-3.2 (75.3)
SE	8.5	15.1
Median	0.3	-24.0
Min, Max	-175, 221	-108, 132

mBMI value = albumin (g/L) x weight (kg) / height (m)^2; higher values indicate higher nutritional status. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

Alnylam Pharmaceuticals Inc.
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Table 5.3
Modified Body Mass Index (mBMI): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Sex: Male

Subgroup Visit	Vutrisiran (HELIOS-A) (N=79)	Patisiran (HELIOS-A) (N=27)
Month 9		
Actual Value		
n	74	24
Mean (SD)	1064.7 (233.2)	1075.9 (202.6)
SE	27.1	41.4
Median	1051.7	1064.4
Min, Max	587, 1747	726, 1626
Change from baseline		
n	74	24
Mean (SD)	8.0 (77.4)	-11.4 (83.9)
SE	9.0	17.1
Median	-5.3	-12.4
Min, Max	-218, 198	-145, 151

mBMI value = albumin (g/L) x weight (kg) / height (m)^2; higher values indicate higher nutritional status. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

Alnylam Pharmaceuticals Inc.
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Table 5.3
Modified Body Mass Index (mBMI): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Sex: Male

Subgroup Visit	Vutrisiran (HELIOS-A) (N=79)	Patisiran (HELIOS-A) (N=27)
Day 337		
Actual Value		
n	74	25
Mean (SD)	1068.2 (225.8)	1056.2 (176.2)
SE	26.2	35.2
Median	1028.2	1056.5
Min, Max	669, 1812	768, 1584
Change from baseline		
n	74	25
Mean (SD)	11.8 (74.7)	-19.4 (89.9)
SE	8.7	18.0
Median	5.6	-34.9
Min, Max	-162, 190	-187, 131

mBMI value = albumin (g/L) x weight (kg) / height (m)^2; higher values indicate higher nutritional status. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

Alnylam Pharmaceuticals Inc.
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Table 5.3
Modified Body Mass Index (mBMI): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Sex: Male

Subgroup Visit	Vutrisiran (HELIOS-A) (N=79)	Patisiran (HELIOS-A) (N=27)
Day 421		
Actual Value		
n	76	23
Mean (SD)	1081.7 (241.4)	1061.2 (190.1)
SE	27.7	39.6
Median	1066.3	1050.4
Min, Max	660, 1877	780, 1557
Change from baseline		
n	76	23
Mean (SD)	21.0 (89.9)	0.3 (72.6)
SE	10.3	15.1
Median	15.4	-14.9
Min, Max	-166, 215	-162, 160

mBMI value = albumin (g/L) x weight (kg) / height (m)^2; higher values indicate higher nutritional status. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Alnylam Pharmaceuticals Inc.
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Table 5.3
Modified Body Mass Index (mBMI): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Sex: Male

Subgroup Visit	Vutrisiran (HELIOS-A) (N=79)	Patisiran (HELIOS-A) (N=27)
Day 505		
Actual Value		
n	75	23
Mean (SD)	1078.9 (233.3)	1061.9 (201.3)
SE	26.9	42.0
Median	1046.4	1060.0
Min, Max	598, 1858	683, 1558
Change from baseline		
n	75	23
Mean (SD)	20.2 (100.0)	0.9 (84.2)
SE	11.5	17.6
Median	33.6	-1.2
Min, Max	-236, 307	-138, 187

mBMI value = albumin (g/L) x weight (kg) / height (m)^2; higher values indicate higher nutritional status. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Alnylam Pharmaceuticals Inc.
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Table 5.3
Modified Body Mass Index (mBMI): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Sex: Male

Subgroup Visit	Vutrisiran (HELIOS-A) (N=79)	Patisiran (HELIOS-A) (N=27)
Month 18		
Actual Value		
n	74	23
Mean (SD)	1087.5 (242.0)	1066.0 (186.1)
SE	28.1	38.8
Median	1054.4	1073.5
Min, Max	572, 2120	766, 1593
Change from baseline		
n	74	23
Mean (SD)	22.0 (106.0)	5.1 (76.3)
SE	12.3	15.9
Median	15.4	0.0
Min, Max	-216, 397	-143, 179

mBMI value = albumin (g/L) x weight (kg) / height (m)^2; higher values indicate higher nutritional status. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

Alnylam Pharmaceuticals Inc.
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Table 5.3
Modified Body Mass Index (mBMI): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Sex: Female

Subgroup Visit	Vutrisiran (HELIOS-A) (N=43)	Patisiran (HELIOS-A) (N=15)
Baseline		
n	43	15
Mean (SD)	1058.2 (266.2)	1025.6 (282.0)
SE	40.6	72.8
Median	1028.4	925.0
Min, Max	589, 1533	646, 1534
Day 85		
Actual Value		
n	41	13
Mean (SD)	1060.4 (255.7)	993.2 (285.5)
SE	39.9	79.2
Median	1016.5	900.3
Min, Max	667, 1551	590, 1570
Change from baseline		
n	41	13
Mean (SD)	1.7 (64.1)	-28.6 (72.9)
SE	10.0	20.2
Median	4.0	-33.4
Min, Max	-132, 144	-183, 63

mBMI value = albumin (g/L) x weight (kg) / height (m)^2; higher values indicate higher nutritional status. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 5.3
Modified Body Mass Index (mBMI): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Sex: Female

Subgroup Visit	Vutrisiran (HELIOS-A) (N=43)	Patisiran (HELIOS-A) (N=15)
Day 169		
Actual Value		
n	43	13
Mean (SD)	1069.3 (254.8)	1007.3 (293.6)
SE	38.9	81.4
Median	1041.3	913.5
Min, Max	599, 1585	583, 1484
Change from baseline		
n	43	13
Mean (SD)	11.0 (72.6)	-38.3 (69.7)
SE	11.1	19.3
Median	20.3	-54.4
Min, Max	-159, 191	-168, 105

mBMI value = albumin (g/L) x weight (kg) / height (m)^2; higher values indicate higher nutritional status. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 5.3
Modified Body Mass Index (mBMI): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Sex: Female

Subgroup Visit	Vutrisiran (HELIOS-A) (N=43)	Patisiran (HELIOS-A) (N=15)
Month 9		
Actual Value		
n	40	14
Mean (SD)	1059.3 (243.3)	1051.5 (355.5)
SE	38.5	95.0
Median	1029.2	900.3
Min, Max	649, 1576	584, 1634
Change from baseline		
n	40	14
Mean (SD)	-6.8 (67.9)	8.0 (133.3)
SE	10.7	35.6
Median	-2.9	23.3
Min, Max	-177, 112	-369, 169

mBMI value = albumin (g/L) x weight (kg) / height (m)^2; higher values indicate higher nutritional status. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 5.3
Modified Body Mass Index (mBMI): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Sex: Female

Subgroup Visit	Vutrisiran (HELIOS-A) (N=43)	Patisiran (HELIOS-A) (N=15)
Day 337		
Actual Value		
n	42	15
Mean (SD)	1080.6 (236.1)	996.6 (295.4)
SE	36.4	76.3
Median	1074.7	937.5
Min, Max	705, 1587	601, 1547
Change from baseline		
n	42	15
Mean (SD)	13.7 (74.0)	-29.0 (98.9)
SE	11.4	25.5
Median	21.5	-24.9
Min, Max	-162, 182	-317, 90

mBMI value = albumin (g/L) x weight (kg) / height (m)^2; higher values indicate higher nutritional status. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 5.3
Modified Body Mass Index (mBMI): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Sex: Female

Subgroup Visit	Vutrisiran (HELIOS-A) (N=43)	Patisiran (HELIOS-A) (N=15)
Day 421		
Actual Value		
n	42	14
Mean (SD)	1091.8 (250.9)	1014.4 (316.1)
SE	38.7	84.5
Median	1064.1	907.5
Min, Max	697, 1661	635, 1553
Change from baseline		
n	42	14
Mean (SD)	24.9 (95.2)	-29.1 (118.3)
SE	14.7	31.6
Median	7.5	8.7
Min, Max	-138, 228	-388, 66

mBMI value = albumin (g/L) x weight (kg) / height (m)^2; higher values indicate higher nutritional status. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 5.3
Modified Body Mass Index (mBMI): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Sex: Female

Subgroup Visit	Vutrisiran (HELIOS-A) (N=43)	Patisiran (HELIOS-A) (N=15)
Day 505		
Actual Value		
n	42	14
Mean (SD)	1097.3 (257.1)	1024.5 (303.5)
SE	39.7	81.1
Median	1067.4	943.0
Min, Max	701, 1781	662, 1607
Change from baseline		
n	42	14
Mean (SD)	30.3 (93.6)	-11.8 (120.2)
SE	14.4	32.1
Median	18.8	-17.9
Min, Max	-130, 249	-290, 180

mBMI value = albumin (g/L) x weight (kg) / height (m)^2; higher values indicate higher nutritional status. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 5.3
Modified Body Mass Index (mBMI): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Sex: Female

Subgroup Visit	Vutrisiran (HELIOS-A) (N=43)	Patisiran (HELIOS-A) (N=15)
Month 18		
Actual Value		
n	41	15
Mean (SD)	1081.1 (247.1)	1035.3 (306.0)
SE	38.6	79.0
Median	1051.2	896.3
Min, Max	652, 1693	652, 1579
Change from baseline		
n	41	15
Mean (SD)	24.8 (94.9)	9.7 (114.5)
SE	14.8	29.6
Median	34.2	-6.1
Min, Max	-150, 203	-284, 171

mBMI value = albumin (g/L) x weight (kg) / height (m)^2; higher values indicate higher nutritional status. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

Alnylam Pharmaceuticals Inc.
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Table 5.3
Modified Body Mass Index (mBMI): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Race: White

Subgroup Visit	Vutrisiran (HELIOS-A) (N=86)	Patisiran (HELIOS-A) (N=29)
Baseline		
n	86	29
Mean (SD)	1090.2 (224.2)	1074.3 (237.6)
SE	24.2	44.1
Median	1063.8	1033.7
Min, Max	705, 1723	646, 1636
Day 85		
Actual Value		
n	79	26
Mean (SD)	1094.6 (214.0)	1060.4 (240.4)
SE	24.1	47.2
Median	1053.9	1026.8
Min, Max	742, 1750	590, 1570
Change from baseline		
n	79	26
Mean (SD)	-2.8 (79.9)	-13.3 (64.9)
SE	9.0	12.7
Median	3.3	-18.1
Min, Max	-295, 180	-183, 83

mBMI value = albumin (g/L) x weight (kg) / height (m)^2; higher values indicate higher nutritional status. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 5.3
Modified Body Mass Index (mBMI): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Race: White

Subgroup Visit	Vutrisiran (HELIOS-A) (N=86)	Patisiran (HELIOS-A) (N=29)
Day 169		
Actual Value		
n	83	27
Mean (SD)	1090.2 (214.3)	1069.9 (231.8)
SE	23.5	44.6
Median	1055.1	1077.3
Min, Max	692, 1778	583, 1578
Change from baseline		
n	83	27
Mean (SD)	-0.2 (73.1)	-9.8 (81.2)
SE	8.0	15.6
Median	0.0	-24.0
Min, Max	-175, 221	-168, 132

mBMI value = albumin (g/L) x weight (kg) / height (m)^2; higher values indicate higher nutritional status. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Alnylam Pharmaceuticals Inc.
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Table 5.3
Modified Body Mass Index (mBMI): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Race: White

Subgroup Visit	Vutrisiran (HELIOS-A) (N=86)	Patisiran (HELIOS-A) (N=29)
Month 9		
Actual Value		
n	81	27
Mean (SD)	1093.0 (227.7)	1090.0 (278.7)
SE	25.3	53.6
Median	1072.9	1061.7
Min, Max	729, 1747	584, 1634
Change from baseline		
n	81	27
Mean (SD)	-0.5 (76.8)	7.0 (114.4)
SE	8.5	22.0
Median	-5.9	5.2
Min, Max	-218, 198	-369, 169

mBMI value = albumin (g/L) x weight (kg) / height (m)^2; higher values indicate higher nutritional status. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 5.3
Modified Body Mass Index (mBMI): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Race: White

Subgroup Visit	Vutrisiran (HELIOS-A) (N=86)	Patisiran (HELIOS-A) (N=29)
Day 337		
Actual Value		
n	82	28
Mean (SD)	1092.0 (221.4)	1057.2 (241.2)
SE	24.5	45.6
Median	1073.8	1055.2
Min, Max	688, 1812	601, 1584
Change from baseline		
n	82	28
Mean (SD)	0.4 (71.1)	-14.8 (90.9)
SE	7.9	17.2
Median	-6.5	-20.9
Min, Max	-162, 190	-317, 131

mBMI value = albumin (g/L) x weight (kg) / height (m)^2; higher values indicate higher nutritional status. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 5.3
Modified Body Mass Index (mBMI): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Race: White

Subgroup Visit	Vutrisiran (HELIOS-A) (N=86)	Patisiran (HELIOS-A) (N=29)
Day 421		
Actual Value		
n	84	26
Mean (SD)	1104.7 (232.6)	1071.5 (254.7)
SE	25.4	49.9
Median	1078.9	1050.7
Min, Max	662, 1877	635, 1557
Change from baseline		
n	84	26
Mean (SD)	11.0 (90.6)	-12.5 (102.3)
SE	9.9	20.1
Median	2.8	-2.8
Min, Max	-166, 190	-388, 160

mBMI value = albumin (g/L) x weight (kg) / height (m)^2; higher values indicate higher nutritional status. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 5.3
Modified Body Mass Index (mBMI): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Race: White

Subgroup Visit	Vutrisiran (HELIOS-A) (N=86)	Patisiran (HELIOS-A) (N=29)
Day 505		
Actual Value		
n	82	26
Mean (SD)	1111.8 (227.3)	1098.1 (252.8)
SE	25.1	49.6
Median	1117.3	1110.7
Min, Max	690, 1858	662, 1607
Change from baseline		
n	82	26
Mean (SD)	18.3 (102.1)	18.0 (104.8)
SE	11.3	20.6
Median	24.9	21.0
Min, Max	-236, 307	-290, 187

mBMI value = albumin (g/L) x weight (kg) / height (m)^2; higher values indicate higher nutritional status. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 5.3
Modified Body Mass Index (mBMI): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Race: White

Subgroup Visit	Vutrisiran (HELIOS-A) (N=86)	Patisiran (HELIOS-A) (N=29)
Month 18		
Actual Value		
n	82	27
Mean (SD)	1114.4 (237.1)	1097.2 (247.2)
SE	26.2	47.6
Median	1068.4	1074.4
Min, Max	711, 2120	652, 1593
Change from baseline		
n	82	27
Mean (SD)	17.7 (109.1)	24.6 (97.4)
SE	12.0	18.7
Median	15.1	28.1
Min, Max	-216, 397	-284, 179

mBMI value = albumin (g/L) x weight (kg) / height (m)^2; higher values indicate higher nutritional status. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 5.3
Modified Body Mass Index (mBMI): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Race: All Other Races

Subgroup Visit	Vutrisiran (HELIOS-A) (N=36)	Patisiran (HELIOS-A) (N=13)
Baseline		
n	36	13
Mean (SD)	979.0 (240.5)	1022.0 (212.4)
SE	40.1	58.9
Median	944.6	1022.7
Min, Max	589, 1533	695, 1431
Day 85		
Actual Value		
n	36	13
Mean (SD)	985.7 (224.6)	1009.4 (209.3)
SE	37.4	58.0
Median	934.1	1037.1
Min, Max	667, 1536	758, 1417
Change from baseline		
n	36	13
Mean (SD)	6.8 (64.2)	-12.6 (82.2)
SE	10.7	22.8
Median	7.2	-13.6
Min, Max	-150, 144	-148, 108

mBMI value = albumin (g/L) x weight (kg) / height (m)^2; higher values indicate higher nutritional status. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 5.3
Modified Body Mass Index (mBMI): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Race: All Other Races

Subgroup Visit	Vutrisiran (HELIOS-A) (N=36)	Patisiran (HELIOS-A) (N=13)
Day 169		
Actual Value		
n	35	11
Mean (SD)	996.3 (256.5)	1001.4 (219.4)
SE	43.4	66.2
Median	910.1	940.5
Min, Max	599, 1585	718, 1449
Change from baseline		
n	35	11
Mean (SD)	18.0 (73.0)	-28.7 (55.1)
SE	12.3	16.6
Median	19.0	-36.4
Min, Max	-159, 191	-104, 85

mBMI value = albumin (g/L) x weight (kg) / height (m)^2; higher values indicate higher nutritional status. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 5.3
Modified Body Mass Index (mBMI): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Race: All Other Races

Subgroup Visit	Vutrisiran (HELIOS-A) (N=36)	Patisiran (HELIOS-A) (N=13)
Month 9		
Actual Value		
n	33	11
Mean (SD)	988.7 (242.1)	1010.1 (228.7)
SE	42.1	69.0
Median	951.2	948.6
Min, Max	587, 1576	758, 1451
Change from baseline		
n	33	11
Mean (SD)	11.1 (68.0)	-31.8 (66.2)
SE	11.8	20.0
Median	20.6	-41.1
Min, Max	-177, 145	-145, 63

mBMI value = albumin (g/L) x weight (kg) / height (m)^2; higher values indicate higher nutritional status. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 5.3
Modified Body Mass Index (mBMI): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Race: All Other Races

Subgroup Visit	Vutrisiran (HELIOS-A) (N=36)	Patisiran (HELIOS-A) (N=13)
Day 337		
Actual Value		
n	34	12
Mean (SD)	1026.2 (242.2)	979.2 (185.6)
SE	41.5	53.6
Median	949.8	936.7
Min, Max	669, 1587	747, 1324
Change from baseline		
n	34	12
Mean (SD)	41.6 (74.1)	-42.1 (96.3)
SE	12.7	27.8
Median	42.6	-89.6
Min, Max	-103, 182	-187, 86

mBMI value = albumin (g/L) x weight (kg) / height (m)^2; higher values indicate higher nutritional status. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 5.3
Modified Body Mass Index (mBMI): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Race: All Other Races

Subgroup Visit	Vutrisiran (HELIOS-A) (N=36)	Patisiran (HELIOS-A) (N=13)
Day 421		
Actual Value		
n	34	11
Mean (SD)	1037.4 (266.9)	977.1 (205.6)
SE	45.8	62.0
Median	935.1	917.1
Min, Max	660, 1661	761, 1467
Change from baseline		
n	34	11
Mean (SD)	50.6 (88.6)	-6.9 (66.2)
SE	15.2	20.0
Median	31.7	-12.5
Min, Max	-142, 228	-162, 83

mBMI value = albumin (g/L) x weight (kg) / height (m)^2; higher values indicate higher nutritional status. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 5.3
Modified Body Mass Index (mBMI): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Race: All Other Races

Subgroup Visit	Vutrisiran (HELIOS-A) (N=36)	Patisiran (HELIOS-A) (N=13)
Day 505		
Actual Value		
n	35	11
Mean (SD)	1023.9 (264.2)	928.6 (167.6)
SE	44.7	50.5
Median	965.7	916.1
Min, Max	598, 1781	727, 1329
Change from baseline		
n	35	11
Mean (SD)	36.7 (85.7)	-55.5 (53.8)
SE	14.5	16.2
Median	45.7	-77.9
Min, Max	-137, 249	-138, 31

mBMI value = albumin (g/L) x weight (kg) / height (m)^2; higher values indicate higher nutritional status. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 5.3
Modified Body Mass Index (mBMI): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Race: All Other Races

Subgroup Visit	Vutrisiran (HELIOS-A) (N=36)	Patisiran (HELIOS-A) (N=13)
Month 18		
Actual Value		
n	33	11
Mean (SD)	1012.7 (244.9)	947.6 (178.2)
SE	42.6	53.7
Median	919.6	931.8
Min, Max	572, 1535	742, 1360
Change from baseline		
n	33	11
Mean (SD)	36.2 (80.8)	-36.5 (60.1)
SE	14.1	18.1
Median	35.1	-35.7
Min, Max	-94, 252	-143, 69

mBMI value = albumin (g/L) x weight (kg) / height (m)^2; higher values indicate higher nutritional status. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 5.3
Modified Body Mass Index (mBMI): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Region: North America

Subgroup Visit	Vutrisiran (HELIOS-A) (N=27)	Patisiran (HELIOS-A) (N=8)
Baseline		
n	27	8
Mean (SD)	1201.5 (204.7)	1235.6 (297.5)
SE	39.4	105.2
Median	1122.8	1287.9
Min, Max	715, 1667	795, 1636
Day 85		
Actual Value		
n	24	7
Mean (SD)	1203.3 (215.1)	1216.3 (283.7)
SE	43.9	107.2
Median	1173.1	1291.1
Min, Max	790, 1551	825, 1569
Change from baseline		
n	24	7
Mean (SD)	-15.0 (82.8)	-41.8 (70.8)
SE	16.9	26.8
Median	11.8	-30.3
Min, Max	-190, 114	-183, 31

mBMI value = albumin (g/L) x weight (kg) / height (m)^2; higher values indicate higher nutritional status. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 5.3
Modified Body Mass Index (mBMI): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Region: North America

Subgroup Visit	Vutrisiran (HELIOS-A) (N=27)	Patisiran (HELIOS-A) (N=8)
Day 169		
Actual Value		
n	26	8
Mean (SD)	1208.2 (206.7)	1215.4 (296.8)
SE	40.5	104.9
Median	1209.4	1288.6
Min, Max	799, 1585	707, 1578
Change from baseline		
n	26	8
Mean (SD)	12.7 (83.1)	-20.2 (79.1)
SE	16.3	28.0
Median	18.1	0.7
Min, Max	-154, 221	-168, 85

mBMI value = albumin (g/L) x weight (kg) / height (m)^2; higher values indicate higher nutritional status. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 5.3
Modified Body Mass Index (mBMI): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Region: North America

Subgroup Visit	Vutrisiran (HELIOS-A) (N=27)	Patisiran (HELIOS-A) (N=8)
Month 9		
Actual Value		
n	23	7
Mean (SD)	1257.4 (205.4)	1333.0 (278.7)
SE	42.8	105.3
Median	1242.6	1385.5
Min, Max	779, 1658	828, 1634
Change from baseline		
n	23	7
Mean (SD)	40.8 (64.0)	34.4 (111.2)
SE	13.3	42.0
Median	64.4	-10.6
Min, Max	-83, 174	-103, 169

mBMI value = albumin (g/L) x weight (kg) / height (m)^2; higher values indicate higher nutritional status. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 5.3
Modified Body Mass Index (mBMI): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Region: North America

Subgroup Visit	Vutrisiran (HELIOS-A) (N=27)	Patisiran (HELIOS-A) (N=8)
Day 337		
Actual Value		
n	24	8
Mean (SD)	1224.0 (192.1)	1206.1 (263.9)
SE	39.2	93.3
Median	1215.1	1217.0
Min, Max	814, 1513	827, 1584
Change from baseline		
n	24	8
Mean (SD)	15.3 (85.1)	-29.5 (93.7)
SE	17.4	33.1
Median	19.1	-37.0
Min, Max	-153, 180	-187, 90

mBMI value = albumin (g/L) x weight (kg) / height (m)^2; higher values indicate higher nutritional status. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 5.3
Modified Body Mass Index (mBMI): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Region: North America

Subgroup Visit	Vutrisiran (HELIOS-A) (N=27)	Patisiran (HELIOS-A) (N=8)
Day 421		
Actual Value		
n	27	7
Mean (SD)	1240.6 (203.6)	1212.9 (305.5)
SE	39.2	115.5
Median	1229.4	1274.0
Min, Max	808, 1591	780, 1557
Change from baseline		
n	27	7
Mean (SD)	39.1 (101.5)	5.2 (50.6)
SE	19.5	19.1
Median	63.8	-1.6
Min, Max	-145, 181	-79, 86

mBMI value = albumin (g/L) x weight (kg) / height (m)^2; higher values indicate higher nutritional status. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 5.3
Modified Body Mass Index (mBMI): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Region: North America

Subgroup Visit	Vutrisiran (HELIOS-A) (N=27)	Patisiran (HELIOS-A) (N=8)
Day 505		
Actual Value		
n	25	6
Mean (SD)	1251.1 (180.2)	1269.1 (265.0)
SE	36.0	108.2
Median	1213.8	1282.0
Min, Max	829, 1572	794, 1558
Change from baseline		
n	25	6
Mean (SD)	41.7 (102.1)	6.1 (90.4)
SE	20.4	36.9
Median	48.4	-14.1
Min, Max	-236, 215	-78, 180

mBMI value = albumin (g/L) x weight (kg) / height (m)^2; higher values indicate higher nutritional status. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 5.3
Modified Body Mass Index (mBMI): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Region: North America

Subgroup Visit	Vutrisiran (HELIOS-A) (N=27)	Patisiran (HELIOS-A) (N=8)
Month 18		
Actual Value		
n	25	7
Mean (SD)	1235.9 (205.6)	1251.8 (290.8)
SE	41.1	109.9
Median	1235.9	1263.1
Min, Max	852, 1693	864, 1593
Change from baseline		
n	25	7
Mean (SD)	47.2 (88.7)	44.1 (92.5)
SE	17.7	35.0
Median	74.4	-6.1
Min, Max	-115, 189	-43, 171

mBMI value = albumin (g/L) x weight (kg) / height (m)^2; higher values indicate higher nutritional status. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 5.3
Modified Body Mass Index (mBMI): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Region: Western Europe

Subgroup Visit	Vutrisiran (HELIOS-A) (N=42)	Patisiran (HELIOS-A) (N=20)
Baseline		
n	42	20
Mean (SD)	1063.7 (211.9)	1031.4 (209.2)
SE	32.7	46.8
Median	1035.5	1025.4
Min, Max	712, 1723	646, 1534
Day 85		
Actual Value		
n	39	19
Mean (SD)	1082.0 (199.6)	1022.5 (227.8)
SE	32.0	52.3
Median	1045.8	1023.8
Min, Max	758, 1750	590, 1570
Change from baseline		
n	39	19
Mean (SD)	6.2 (80.4)	-3.3 (68.4)
SE	12.9	15.7
Median	3.1	6.5
Min, Max	-144, 180	-153, 97

mBMI value = albumin (g/L) x weight (kg) / height (m)^2; higher values indicate higher nutritional status. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 5.3
Modified Body Mass Index (mBMI): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Region: Western Europe

Subgroup Visit	Vutrisiran (HELIOS-A) (N=42)	Patisiran (HELIOS-A) (N=20)
Day 169		
Actual Value		
n	39	16
Mean (SD)	1062.5 (211.2)	1022.3 (212.4)
SE	33.8	53.1
Median	1041.3	1056.1
Min, Max	772, 1778	583, 1484
Change from baseline		
n	39	16
Mean (SD)	-9.0 (73.2)	-19.5 (68.7)
SE	11.7	17.2
Median	-6.2	-39.6
Min, Max	-152, 186	-108, 132

mBMI value = albumin (g/L) x weight (kg) / height (m)^2; higher values indicate higher nutritional status. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 5.3
Modified Body Mass Index (mBMI): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Region: Western Europe

Subgroup Visit	Vutrisiran (HELIOS-A) (N=42)	Patisiran (HELIOS-A) (N=20)
Month 9		
Actual Value		
n	39	18
Mean (SD)	1055.3 (213.4)	1035.6 (243.0)
SE	34.2	57.3
Median	1040.9	1053.8
Min, Max	729, 1747	584, 1633
Change from baseline		
n	39	18
Mean (SD)	-13.0 (81.3)	10.2 (85.7)
SE	13.0	20.2
Median	-26.4	-3.6
Min, Max	-149, 198	-129, 151

mBMI value = albumin (g/L) x weight (kg) / height (m)^2; higher values indicate higher nutritional status. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 5.3
Modified Body Mass Index (mBMI): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Region: Western Europe

Subgroup Visit	Vutrisiran (HELIOS-A) (N=42)	Patisiran (HELIOS-A) (N=20)
Day 337		
Actual Value		
n	40	18
Mean (SD)	1079.8 (213.5)	1025.2 (211.6)
SE	33.8	49.9
Median	1055.0	1021.4
Min, Max	747, 1812	601, 1547
Change from baseline		
n	40	18
Mean (SD)	10.2 (81.3)	-0.3 (76.2)
SE	12.8	18.0
Median	15.5	-2.2
Min, Max	-162, 190	-108, 131

mBMI value = albumin (g/L) x weight (kg) / height (m)^2; higher values indicate higher nutritional status. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 5.3
Modified Body Mass Index (mBMI): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Region: Western Europe

Subgroup Visit	Vutrisiran (HELIOS-A) (N=42)	Patisiran (HELIOS-A) (N=20)
Day 421		
Actual Value		
n	39	18
Mean (SD)	1083.2 (223.2)	1023.8 (212.0)
SE	35.7	50.0
Median	1056.7	1027.4
Min, Max	703, 1877	683, 1553
Change from baseline		
n	39	18
Mean (SD)	11.7 (88.0)	-1.7 (73.2)
SE	14.1	17.2
Median	-2.3	-5.9
Min, Max	-141, 200	-162, 160

mBMI value = albumin (g/L) x weight (kg) / height (m)^2; higher values indicate higher nutritional status. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 5.3
Modified Body Mass Index (mBMI): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Region: Western Europe

Subgroup Visit	Vutrisiran (HELIOS-A) (N=42)	Patisiran (HELIOS-A) (N=20)
Day 505		
Actual Value		
n	40	18
Mean (SD)	1089.8 (219.1)	1059.2 (233.9)
SE	34.6	55.1
Median	1066.0	1067.2
Min, Max	744, 1858	662, 1607
Change from baseline		
n	40	18
Mean (SD)	20.1 (96.4)	33.7 (85.8)
SE	15.2	20.2
Median	22.6	26.2
Min, Max	-222, 307	-108, 187

mBMI value = albumin (g/L) x weight (kg) / height (m)^2; higher values indicate higher nutritional status. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 5.3
Modified Body Mass Index (mBMI): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Region: Western Europe

Subgroup Visit	Vutrisiran (HELIOS-A) (N=42)	Patisiran (HELIOS-A) (N=20)
Month 18		
Actual Value		
n	40	18
Mean (SD)	1095.2 (243.9)	1050.7 (215.5)
SE	38.6	50.8
Median	1051.1	1051.4
Min, Max	738, 2120	652, 1579
Change from baseline		
n	40	18
Mean (SD)	25.5 (111.5)	25.2 (73.7)
SE	17.6	17.4
Median	4.4	27.2
Min, Max	-187, 397	-108, 179

mBMI value = albumin (g/L) x weight (kg) / height (m)^2; higher values indicate higher nutritional status. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 5.3
Modified Body Mass Index (mBMI): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Region: Rest of World

Subgroup Visit	Vutrisiran (HELIOS-A) (N=53)	Patisiran (HELIOS-A) (N=14)
Baseline		
n	53	14
Mean (SD)	978.9 (231.8)	994.9 (169.3)
SE	31.8	45.3
Median	947.1	1022.7
Min, Max	589, 1533	695, 1414
Day 85		
Actual Value		
n	52	13
Mean (SD)	978.5 (207.5)	980.8 (160.2)
SE	28.8	44.4
Median	935.1	1037.1
Min, Max	667, 1606	758, 1314
Change from baseline		
n	52	13
Mean (SD)	2.7 (67.8)	-12.0 (73.3)
SE	9.4	20.3
Median	3.3	-15.1
Min, Max	-295, 128	-148, 108

mBMI value = albumin (g/L) x weight (kg) / height (m)^2; higher values indicate higher nutritional status. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 5.3
Modified Body Mass Index (mBMI): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Region: Rest of World

Subgroup Visit	Vutrisiran (HELIOS-A) (N=53)	Patisiran (HELIOS-A) (N=14)
Day 169		
Actual Value		
n	53	14
Mean (SD)	990.8 (225.0)	987.4 (160.6)
SE	30.9	42.9
Median	921.1	955.5
Min, Max	599, 1546	718, 1351
Change from baseline		
n	53	14
Mean (SD)	11.9 (67.9)	-7.5 (82.6)
SE	9.3	22.1
Median	9.1	-34.1
Min, Max	-175, 157	-109, 129

mBMI value = albumin (g/L) x weight (kg) / height (m)^2; higher values indicate higher nutritional status. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 5.3
Modified Body Mass Index (mBMI): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Region: Rest of World

Subgroup Visit	Vutrisiran (HELIOS-A) (N=53)	Patisiran (HELIOS-A) (N=14)
Month 9		
Actual Value		
n	52	13
Mean (SD)	982.4 (217.4)	966.9 (199.9)
SE	30.1	55.4
Median	944.7	948.6
Min, Max	587, 1550	654, 1451
Change from baseline		
n	52	13
Mean (SD)	-2.1 (68.2)	-45.0 (115.9)
SE	9.5	32.2
Median	-4.0	5.2
Min, Max	-218, 145	-369, 63

mBMI value = albumin (g/L) x weight (kg) / height (m)^2; higher values indicate higher nutritional status. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

Alnylam Pharmaceuticals Inc.
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Table 5.3
Modified Body Mass Index (mBMI): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Region: Rest of World

Subgroup Visit	Vutrisiran (HELIOS-A) (N=53)	Patisiran (HELIOS-A) (N=14)
Day 337		
Actual Value		
n	52	14
Mean (SD)	997.4 (223.1)	946.4 (176.8)
SE	30.9	47.2
Median	939.4	928.6
Min, Max	669, 1587	705, 1324
Change from baseline		
n	52	14
Mean (SD)	12.9 (63.7)	-48.5 (108.3)
SE	8.8	29.0
Median	3.9	-61.7
Min, Max	-103, 182	-317, 85

mBMI value = albumin (g/L) x weight (kg) / height (m)^2; higher values indicate higher nutritional status. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

Alnylam Pharmaceuticals Inc.
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Table 5.3
Modified Body Mass Index (mBMI): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Region: Rest of World

Subgroup Visit	Vutrisiran (HELIOS-A) (N=53)	Patisiran (HELIOS-A) (N=14)
Day 421		
Actual Value		
n	52	12
Mean (SD)	1006.2 (242.7)	974.2 (218.2)
SE	33.7	63.0
Median	948.1	944.1
Min, Max	660, 1661	635, 1467
Change from baseline		
n	52	12
Mean (SD)	21.7 (89.0)	-34.0 (131.2)
SE	12.3	37.9
Median	14.7	-16.3
Min, Max	-166, 228	-388, 83

mBMI value = albumin (g/L) x weight (kg) / height (m)^2; higher values indicate higher nutritional status. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 5.3
Modified Body Mass Index (mBMI): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Region: Rest of World

Subgroup Visit	Vutrisiran (HELIOS-A) (N=53)	Patisiran (HELIOS-A) (N=14)
Day 505		
Actual Value		
n	52	13
Mean (SD)	1002.6 (244.7)	929.7 (168.6)
SE	33.9	46.8
Median	959.7	895.5
Min, Max	598, 1781	727, 1329
Change from baseline		
n	52	13
Mean (SD)	18.1 (96.9)	-60.5 (96.4)
SE	13.4	26.7
Median	13.9	-77.9
Min, Max	-194, 249	-290, 74

mBMI value = albumin (g/L) x weight (kg) / height (m)^2; higher values indicate higher nutritional status. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 5.3
Modified Body Mass Index (mBMI): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Region: Rest of World

Subgroup Visit	Vutrisiran (HELIOS-A) (N=53)	Patisiran (HELIOS-A) (N=14)
Month 18		
Actual Value		
n	50	13
Mean (SD)	1001.8 (224.2)	951.8 (176.5)
SE	31.7	49.0
Median	946.8	982.0
Min, Max	572, 1552	739, 1360
Change from baseline		
n	50	13
Mean (SD)	8.8 (99.2)	-38.4 (102.4)
SE	14.0	28.4
Median	15.1	-35.7
Min, Max	-216, 252	-284, 122

mBMI value = albumin (g/L) x weight (kg) / height (m)^2; higher values indicate higher nutritional status. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

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Table 5.3
Modified Body Mass Index (mBMI): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Baseline NIS: <50

Subgroup Visit	Vutrisiran (HELIOS-A) (N=78)	Patisiran (HELIOS-A) (N=27)
Baseline		
n	78	27
Mean (SD)	1104.6 (238.4)	1072.8 (245.1)
SE	27.0	47.2
Median	1115.3	1027.6
Min, Max	589, 1723	646, 1636
Day 85		
Actual Value		
n	76	26
Mean (SD)	1108.8 (226.6)	1048.7 (235.5)
SE	26.0	46.2
Median	1081.7	1026.6
Min, Max	667, 1750	590, 1569
Change from baseline		
n	76	26
Mean (SD)	3.5 (79.3)	-23.9 (71.4)
SE	9.1	14.0
Median	9.8	-25.7
Min, Max	-190, 180	-183, 83

mBMI value = albumin (g/L) x weight (kg) / height (m)^2; higher values indicate higher nutritional status. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

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Table 5.3
Modified Body Mass Index (mBMI): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Baseline NIS: <50

Subgroup Visit	Vutrisiran (HELIOS-A) (N=78)	Patisiran (HELIOS-A) (N=27)
Day 169		
Actual Value		
n	76	27
Mean (SD)	1106.6 (235.7)	1050.4 (241.1)
SE	27.0	46.4
Median	1081.8	1038.1
Min, Max	599, 1778	583, 1578
Change from baseline		
n	76	27
Mean (SD)	4.0 (75.6)	-22.4 (66.4)
SE	8.7	12.8
Median	9.8	-31.8
Min, Max	-159, 221	-168, 132

mBMI value = albumin (g/L) x weight (kg) / height (m)^2; higher values indicate higher nutritional status. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 5.3
Modified Body Mass Index (mBMI): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Baseline NIS: <50

Subgroup Visit	Vutrisiran (HELIOS-A) (N=78)	Patisiran (HELIOS-A) (N=27)
Month 9		
Actual Value		
n	75	25
Mean (SD)	1115.0 (234.0)	1100.8 (273.8)
SE	27.0	54.8
Median	1085.1	1059.8
Min, Max	599, 1747	584, 1634
Change from baseline		
n	75	25
Mean (SD)	6.6 (71.1)	5.0 (96.4)
SE	8.2	19.3
Median	0.0	-21.2
Min, Max	-177, 174	-145, 169

mBMI value = albumin (g/L) x weight (kg) / height (m)^2; higher values indicate higher nutritional status. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 5.3
Modified Body Mass Index (mBMI): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Baseline NIS: <50

Subgroup Visit	Vutrisiran (HELIOS-A) (N=78)	Patisiran (HELIOS-A) (N=27)
Day 337		
Actual Value		
n	75	27
Mean (SD)	1121.8 (230.8)	1044.5 (232.0)
SE	26.6	44.7
Median	1089.1	1025.4
Min, Max	705, 1812	601, 1584
Change from baseline		
n	75	27
Mean (SD)	13.7 (70.6)	-28.2 (81.8)
SE	8.2	15.7
Median	15.0	-44.7
Min, Max	-153, 180	-187, 131

mBMI value = albumin (g/L) x weight (kg) / height (m)^2; higher values indicate higher nutritional status. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 5.3
Modified Body Mass Index (mBMI): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Baseline NIS: <50

Subgroup Visit	Vutrisiran (HELIOS-A) (N=78)	Patisiran (HELIOS-A) (N=27)
Day 421		
Actual Value		
n	76	25
Mean (SD)	1135.8 (241.6)	1059.4 (244.6)
SE	27.7	48.9
Median	1098.7	1050.4
Min, Max	698, 1877	683, 1557
Change from baseline		
n	76	25
Mean (SD)	24.4 (88.0)	-11.0 (67.9)
SE	10.1	13.6
Median	26.6	-12.5
Min, Max	-145, 215	-162, 95

mBMI value = albumin (g/L) x weight (kg) / height (m)^2; higher values indicate higher nutritional status. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 5.3
Modified Body Mass Index (mBMI): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Baseline NIS: <50

Subgroup Visit	Vutrisiran (HELIOS-A) (N=78)	Patisiran (HELIOS-A) (N=27)
Day 505		
Actual Value		
n	75	25
Mean (SD)	1133.7 (240.2)	1069.8 (236.0)
SE	27.7	47.2
Median	1148.1	998.0
Min, Max	614, 1858	662, 1558
Change from baseline		
n	75	25
Mean (SD)	23.5 (92.6)	3.5 (88.2)
SE	10.7	17.6
Median	33.6	-5.1
Min, Max	-236, 249	-108, 187

mBMI value = albumin (g/L) x weight (kg) / height (m)^2; higher values indicate higher nutritional status. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 5.3
Modified Body Mass Index (mBMI): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Baseline NIS: <50

Subgroup Visit	Vutrisiran (HELIOS-A) (N=78)	Patisiran (HELIOS-A) (N=27)
Month 18		
Actual Value		
n	75	26
Mean (SD)	1132.3 (245.0)	1076.5 (239.1)
SE	28.3	46.9
Median	1118.2	1051.4
Min, Max	652, 2120	652, 1593
Change from baseline		
n	75	26
Mean (SD)	29.1 (103.9)	17.5 (82.2)
SE	12.0	16.1
Median	35.1	-3.0
Min, Max	-201, 397	-143, 179

mBMI value = albumin (g/L) x weight (kg) / height (m)^2; higher values indicate higher nutritional status. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 5.3
Modified Body Mass Index (mBMI): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Baseline NIS: ≥50

Subgroup Visit	Vutrisiran (HELIOS-A) (N=44)	Patisiran (HELIOS-A) (N=15)
Baseline		
n	44	15
Mean (SD)	973.7 (202.0)	1031.8 (201.3)
SE	30.5	52.0
Median	965.8	1030.6
Min, Max	634, 1455	658, 1534
Day 85		
Actual Value		
n	39	13
Mean (SD)	966.6 (182.0)	1032.8 (224.5)
SE	29.1	62.3
Median	966.3	1041.4
Min, Max	669, 1407	714, 1570
Change from baseline		
n	39	13
Mean (SD)	-6.2 (67.1)	8.5 (64.5)
SE	10.7	17.9
Median	2.7	8.3
Min, Max	-295, 118	-111, 108

mBMI value = albumin (g/L) x weight (kg) / height (m)^2; higher values indicate higher nutritional status. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 5.3
Modified Body Mass Index (mBMI): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Baseline NIS: ≥50

Subgroup Visit	Vutrisiran (HELIOS-A) (N=44)	Patisiran (HELIOS-A) (N=15)
Day 169		
Actual Value		
n	42	11
Mean (SD)	982.4 (199.8)	1049.3 (200.9)
SE	30.8	60.6
Median	998.1	1043.3
Min, Max	615, 1493	769, 1484
Change from baseline		
n	42	11
Mean (SD)	7.3 (69.6)	2.3 (92.4)
SE	10.7	27.9
Median	1.6	-21.1
Min, Max	-175, 186	-109, 129

mBMI value = albumin (g/L) x weight (kg) / height (m)^2; higher values indicate higher nutritional status. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 5.3
Modified Body Mass Index (mBMI): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Baseline NIS: ≥50

Subgroup Visit	Vutrisiran (HELIOS-A) (N=44)	Patisiran (HELIOS-A) (N=15)
Month 9		
Actual Value		
n	39	13
Mean (SD)	962.4 (207.0)	1001.6 (243.0)
SE	33.2	67.4
Median	946.3	981.6
Min, Max	587, 1550	654, 1633
Change from baseline		
n	39	13
Mean (SD)	-4.5 (80.3)	-22.0 (117.9)
SE	12.9	32.7
Median	-5.8	10.4
Min, Max	-218, 198	-369, 100

mBMI value = albumin (g/L) x weight (kg) / height (m)^2; higher values indicate higher nutritional status. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 5.3
Modified Body Mass Index (mBMI): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Baseline NIS: ≥50

Subgroup Visit	Vutrisiran (HELIOS-A) (N=44)	Patisiran (HELIOS-A) (N=15)
Day 337		
Actual Value		
n	41	13
Mean (SD)	982.8 (197.3)	1011.6 (221.9)
SE	30.8	61.6
Median	941.7	1017.5
Min, Max	669, 1552	705, 1547
Change from baseline		
n	41	13
Mean (SD)	10.2 (81.0)	-12.0 (113.7)
SE	12.6	31.5
Median	5.7	13.4
Min, Max	-162, 190	-317, 123

mBMI value = albumin (g/L) x weight (kg) / height (m)^2; higher values indicate higher nutritional status. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 5.3
Modified Body Mass Index (mBMI): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Baseline NIS: ≥50

Subgroup Visit	Vutrisiran (HELIOS-A) (N=44)	Patisiran (HELIOS-A) (N=15)
Day 421		
Actual Value		
n	42	12
Mean (SD)	993.9 (222.5)	1010.3 (244.6)
SE	34.3	70.6
Median	936.7	978.2
Min, Max	660, 1645	635, 1553
Change from baseline		
n	42	12
Mean (SD)	18.8 (98.3)	-10.6 (133.1)
SE	15.2	38.4
Median	-2.8	6.4
Min, Max	-166, 228	-388, 160

mBMI value = albumin (g/L) x weight (kg) / height (m)^2; higher values indicate higher nutritional status. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 5.3
Modified Body Mass Index (mBMI): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Baseline NIS: ≥50

Subgroup Visit	Vutrisiran (HELIOS-A) (N=44)	Patisiran (HELIOS-A) (N=15)
Day 505		
Actual Value		
n	42	12
Mean (SD)	999.5 (220.5)	1001.7 (256.9)
SE	34.0	74.2
Median	987.1	975.7
Min, Max	598, 1585	683, 1607
Change from baseline		
n	42	12
Mean (SD)	24.4 (106.7)	-19.2 (118.4)
SE	16.5	34.2
Median	14.6	-2.3
Min, Max	-194, 307	-290, 170

mBMI value = albumin (g/L) x weight (kg) / height (m)^2; higher values indicate higher nutritional status. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 5.3
Modified Body Mass Index (mBMI): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Baseline NIS: ≥50

Subgroup Visit	Vutrisiran (HELIOS-A) (N=44)	Patisiran (HELIOS-A) (N=15)
Month 18		
Actual Value		
n	40	12
Mean (SD)	996.8 (214.7)	1004.9 (235.4)
SE	33.9	68.0
Median	940.7	985.7
Min, Max	572, 1446	739, 1579
Change from baseline		
n	40	12
Mean (SD)	11.5 (97.9)	-16.0 (110.3)
SE	15.5	31.8
Median	1.5	-3.1
Min, Max	-216, 203	-284, 124

mBMI value = albumin (g/L) x weight (kg) / height (m)^2; higher values indicate higher nutritional status. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 5.3
Modified Body Mass Index (mBMI): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Previous Tetramer Stabilizer Use: Yes

Subgroup Visit	Vutrisiran (HELIOS-A) (N=75)	Patisiran (HELIOS-A) (N=33)
Baseline		
n	75	33
Mean (SD)	1039.1 (230.2)	1025.9 (201.2)
SE	26.6	35.0
Median	1013.9	1023.2
Min, Max	589, 1723	646, 1534
Day 85		
Actual Value		
n	71	32
Mean (SD)	1042.5 (220.6)	1018.4 (205.8)
SE	26.2	36.4
Median	1016.5	1026.8
Min, Max	669, 1750	590, 1570
Change from baseline		
n	71	32
Mean (SD)	4.7 (80.4)	-7.6 (69.3)
SE	9.5	12.2
Median	9.1	-5.0
Min, Max	-295, 180	-183, 108

mBMI value = albumin (g/L) x weight (kg) / height (m)^2; higher values indicate higher nutritional status. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 5.3
Modified Body Mass Index (mBMI): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Previous Tetramer Stabilizer Use: Yes

Subgroup Visit	Vutrisiran (HELIOS-A) (N=75)	Patisiran (HELIOS-A) (N=33)
Day 169		
Actual Value		
n	73	30
Mean (SD)	1032.2 (224.4)	1012.7 (204.7)
SE	26.3	37.4
Median	1001.4	1028.7
Min, Max	615, 1778	583, 1484
Change from baseline		
n	73	30
Mean (SD)	-0.7 (73.8)	-21.8 (76.5)
SE	8.6	14.0
Median	-2.2	-34.1
Min, Max	-175, 191	-168, 132

mBMI value = albumin (g/L) x weight (kg) / height (m)^2; higher values indicate higher nutritional status. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 5.3
Modified Body Mass Index (mBMI): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Previous Tetramer Stabilizer Use: Yes

Subgroup Visit	Vutrisiran (HELIOS-A) (N=75)	Patisiran (HELIOS-A) (N=33)
Month 9		
Actual Value		
n	74	32
Mean (SD)	1028.9 (228.0)	1023.8 (246.6)
SE	26.5	43.6
Median	1000.1	1027.6
Min, Max	587, 1747	584, 1634
Change from baseline		
n	74	32
Mean (SD)	-8.4 (74.1)	-1.9 (103.6)
SE	8.6	18.3
Median	-18.0	7.8
Min, Max	-218, 198	-369, 151

mBMI value = albumin (g/L) x weight (kg) / height (m)^2; higher values indicate higher nutritional status. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 5.3
Modified Body Mass Index (mBMI): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Previous Tetramer Stabilizer Use: Yes

Subgroup Visit	Vutrisiran (HELIOS-A) (N=75)	Patisiran (HELIOS-A) (N=33)
Day 337		
Actual Value		
n	73	32
Mean (SD)	1047.1 (226.5)	1007.1 (214.1)
SE	26.5	37.9
Median	1017.8	1009.3
Min, Max	669, 1812	601, 1547
Change from baseline		
n	73	32
Mean (SD)	13.4 (68.3)	-18.7 (91.0)
SE	8.0	16.1
Median	13.5	-20.9
Min, Max	-162, 190	-317, 131

mBMI value = albumin (g/L) x weight (kg) / height (m)^2; higher values indicate higher nutritional status. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Alnylam Pharmaceuticals Inc.
ALN-TTRSC02-002

Table 5.3
Modified Body Mass Index (mBMI): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Previous Tetramer Stabilizer Use: Yes

Subgroup Visit	Vutrisiran (HELIOS-A) (N=75)	Patisiran (HELIOS-A) (N=33)
Day 421		
Actual Value		
n	74	31
Mean (SD)	1047.8 (239.3)	1009.9 (219.2)
SE	27.8	39.4
Median	1013.9	1005.7
Min, Max	660, 1877	635, 1553
Change from baseline		
n	74	31
Mean (SD)	10.4 (77.9)	-14.8 (97.4)
SE	9.1	17.5
Median	2.8	-7.9
Min, Max	-166, 168	-388, 160

mBMI value = albumin (g/L) x weight (kg) / height (m)^2; higher values indicate higher nutritional status. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

Alnylam Pharmaceuticals Inc.
ALN-TTRSC02-002

Table 5.3
Modified Body Mass Index (mBMI): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Previous Tetramer Stabilizer Use: Yes

Subgroup Visit	Vutrisiran (HELIOS-A) (N=75)	Patisiran (HELIOS-A) (N=33)
Day 505		
Actual Value		
n	72	30
Mean (SD)	1055.3 (238.5)	1024.5 (228.7)
SE	28.1	41.8
Median	1010.2	995.8
Min, Max	598, 1858	662, 1607
Change from baseline		
n	72	30
Mean (SD)	19.8 (93.4)	-5.2 (99.7)
SE	11.0	18.2
Median	24.9	-7.0
Min, Max	-222, 307	-290, 187

mBMI value = albumin (g/L) x weight (kg) / height (m)^2; higher values indicate higher nutritional status. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

Alnylam Pharmaceuticals Inc.
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Table 5.3
Modified Body Mass Index (mBMI): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Previous Tetramer Stabilizer Use: Yes

Subgroup Visit	Vutrisiran (HELIOS-A) (N=75)	Patisiran (HELIOS-A) (N=33)
Month 18		
Actual Value		
n	71	31
Mean (SD)	1058.6 (257.4)	1027.1 (225.6)
SE	30.6	40.5
Median	1010.9	1005.6
Min, Max	572, 2120	652, 1579
Change from baseline		
n	71	31
Mean (SD)	16.3 (104.8)	2.3 (92.6)
SE	12.4	16.6
Median	3.0	0.0
Min, Max	-216, 397	-284, 179

mBMI value = albumin (g/L) x weight (kg) / height (m)^2; higher values indicate higher nutritional status. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

Alnylam Pharmaceuticals Inc.
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Table 5.3
Modified Body Mass Index (mBMI): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Previous Tetramer Stabilizer Use: No

Subgroup Visit	Vutrisiran (HELIOS-A) (N=47)	Patisiran (HELIOS-A) (N=9)
Baseline		
n	47	9
Mean (SD)	1086.6 (239.0)	1176.2 (293.9)
SE	34.9	98.0
Median	1111.6	1138.4
Min, Max	691, 1667	775, 1636
Day 85		
Actual Value		
n	44	7
Mean (SD)	1089.6 (224.2)	1157.6 (308.0)
SE	33.8	116.4
Median	1097.3	1269.9
Min, Max	667, 1536	825, 1569
Change from baseline		
n	44	7
Mean (SD)	-7.1 (66.3)	-38.1 (73.5)
SE	10.0	27.8
Median	-0.9	-30.3
Min, Max	-190, 144	-148, 63

mBMI value = albumin (g/L) x weight (kg) / height (m)^2; higher values indicate higher nutritional status. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

Alnylam Pharmaceuticals Inc.
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Table 5.3
Modified Body Mass Index (mBMI): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Previous Tetramer Stabilizer Use: No

Subgroup Visit	Vutrisiran (HELIOS-A) (N=47)	Patisiran (HELIOS-A) (N=9)
Day 169		
Actual Value		
n	45	8
Mean (SD)	1111.3 (234.6)	1190.2 (267.5)
SE	35.0	94.6
Median	1084.8	1206.7
Min, Max	599, 1573	879, 1578
Change from baseline		
n	45	8
Mean (SD)	14.6 (72.1)	9.2 (64.4)
SE	10.7	22.8
Median	24.8	6.7
Min, Max	-159, 221	-63, 105

mBMI value = albumin (g/L) x weight (kg) / height (m)^2; higher values indicate higher nutritional status. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

Alnylam Pharmaceuticals Inc.
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Table 5.3
Modified Body Mass Index (mBMI): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Previous Tetramer Stabilizer Use: No

Subgroup Visit	Vutrisiran (HELIOS-A) (N=47)	Patisiran (HELIOS-A) (N=9)
Month 9		
Actual Value		
n	40	6
Mean (SD)	1125.6 (239.8)	1296.4 (257.5)
SE	37.9	105.1
Median	1104.1	1316.3
Min, Max	746, 1658	873, 1626
Change from baseline		
n	40	6
Mean (SD)	23.6 (70.7)	-16.5 (111.5)
SE	11.2	45.5
Median	26.0	-27.9
Min, Max	-177, 174	-145, 169

mBMI value = albumin (g/L) x weight (kg) / height (m)^2; higher values indicate higher nutritional status. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

Alnylam Pharmaceuticals Inc.
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Table 5.3
Modified Body Mass Index (mBMI): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Previous Tetramer Stabilizer Use: No

Subgroup Visit	Vutrisiran (HELIOS-A) (N=47)	Patisiran (HELIOS-A) (N=9)
Day 337		
Actual Value		
n	43	8
Mean (SD)	1116.1 (228.3)	1140.9 (257.6)
SE	34.8	91.1
Median	1132.8	1178.9
Min, Max	688, 1587	817, 1584
Change from baseline		
n	43	8
Mean (SD)	10.9 (83.8)	-40.0 (101.2)
SE	12.8	35.8
Median	12.3	-71.6
Min, Max	-162, 182	-187, 90

mBMI value = albumin (g/L) x weight (kg) / height (m)^2; higher values indicate higher nutritional status. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Alnylam Pharmaceuticals Inc.
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Table 5.3
Modified Body Mass Index (mBMI): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Previous Tetramer Stabilizer Use: No

Subgroup Visit	Vutrisiran (HELIOS-A) (N=47)	Patisiran (HELIOS-A) (N=9)
Day 421		
Actual Value		
n	44	6
Mean (SD)	1148.4 (240.7)	1216.7 (302.1)
SE	36.3	123.3
Median	1170.5	1249.2
Min, Max	662, 1661	780, 1557
Change from baseline		
n	44	6
Mean (SD)	42.5 (108.6)	9.7 (59.4)
SE	16.4	24.2
Median	53.8	9.8
Min, Max	-142, 228	-79, 86

mBMI value = albumin (g/L) x weight (kg) / height (m)^2; higher values indicate higher nutritional status. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 5.3
Modified Body Mass Index (mBMI): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Previous Tetramer Stabilizer Use: No

Subgroup Visit	Vutrisiran (HELIOS-A) (N=47)	Patisiran (HELIOS-A) (N=9)
Day 505		
Actual Value		
n	45	7
Mean (SD)	1133.9 (240.2)	1147.1 (288.2)
SE	35.8	108.9
Median	1143.1	1258.0
Min, Max	690, 1781	794, 1558
Change from baseline		
n	45	7
Mean (SD)	30.3 (104.3)	1.9 (97.4)
SE	15.6	36.8
Median	34.1	-1.2
Min, Max	-236, 249	-86, 180

mBMI value = albumin (g/L) x weight (kg) / height (m)^2; higher values indicate higher nutritional status. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 5.3
Modified Body Mass Index (mBMI): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Previous Tetramer Stabilizer Use: No

Subgroup Visit	Vutrisiran (HELIOS-A) (N=47)	Patisiran (HELIOS-A) (N=9)
Month 18		
Actual Value		
n	44	7
Mean (SD)	1128.1 (212.8)	1172.4 (268.7)
SE	32.1	101.6
Median	1159.0	1248.9
Min, Max	711, 1645	864, 1593
Change from baseline		
n	44	7
Mean (SD)	33.8 (96.9)	27.2 (92.3)
SE	14.6	34.9
Median	38.8	-35.7
Min, Max	-201, 252	-55, 171

mBMI value = albumin (g/L) x weight (kg) / height (m)^2; higher values indicate higher nutritional status. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Alnylam Pharmaceuticals Inc.
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Table 5.3
Modified Body Mass Index (mBMI): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Genotype: V30M

Subgroup Visit	Vutrisiran (HELIOS-A) (N=54)	Patisiran (HELIOS-A) (N=20)
Baseline		
n	54	20
Mean (SD)	1026.5 (209.4)	1005.8 (226.8)
SE	28.5	50.7
Median	1026.6	1023.0
Min, Max	589, 1496	646, 1534
Day 85		
Actual Value		
n	52	19
Mean (SD)	1036.5 (189.6)	996.3 (239.1)
SE	26.3	54.9
Median	1024.4	989.8
Min, Max	717, 1606	590, 1570
Change from baseline		
n	52	19
Mean (SD)	9.0 (72.7)	-5.8 (67.9)
SE	10.1	15.6
Median	9.6	6.5
Min, Max	-132, 180	-153, 83

mBMI value = albumin (g/L) x weight (kg) / height (m)^2; higher values indicate higher nutritional status. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 5.3
Modified Body Mass Index (mBMI): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Genotype: V30M

Subgroup Visit	Vutrisiran (HELIOS-A) (N=54)	Patisiran (HELIOS-A) (N=20)
Day 169		
Actual Value		
n	53	18
Mean (SD)	1028.8 (205.4)	996.3 (215.4)
SE	28.2	50.8
Median	1030.6	1008.6
Min, Max	645, 1493	583, 1484
Change from baseline		
n	53	18
Mean (SD)	5.0 (76.7)	-21.9 (64.7)
SE	10.5	15.3
Median	-2.2	-34.0
Min, Max	-152, 221	-108, 111

mBMI value = albumin (g/L) x weight (kg) / height (m)^2; higher values indicate higher nutritional status. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 5.3
Modified Body Mass Index (mBMI): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Genotype: V30M

Subgroup Visit	Vutrisiran (HELIOS-A) (N=54)	Patisiran (HELIOS-A) (N=20)
Month 9		
Actual Value		
n	51	19
Mean (SD)	1018.1 (214.8)	1022.9 (253.2)
SE	30.1	58.1
Median	1002.1	1001.9
Min, Max	599, 1550	584, 1633
Change from baseline		
n	51	19
Mean (SD)	-2.7 (80.8)	4.9 (91.1)
SE	11.3	20.9
Median	-25.9	-21.2
Min, Max	-149, 198	-129, 169

mBMI value = albumin (g/L) x weight (kg) / height (m)^2; higher values indicate higher nutritional status. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Alnylam Pharmaceuticals Inc.
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Table 5.3
Modified Body Mass Index (mBMI): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Genotype: V30M

Subgroup Visit	Vutrisiran (HELIOS-A) (N=54)	Patisiran (HELIOS-A) (N=20)
Day 337		
Actual Value		
n	51	20
Mean (SD)	1038.1 (207.4)	1008.4 (218.2)
SE	29.0	48.8
Median	1018.8	1021.4
Min, Max	705, 1552	601, 1547
Change from baseline		
n	51	20
Mean (SD)	16.2 (67.3)	2.5 (72.1)
SE	9.4	16.1
Median	12.3	12.9
Min, Max	-162, 190	-108, 123

mBMI value = albumin (g/L) x weight (kg) / height (m)^2; higher values indicate higher nutritional status. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Alnylam Pharmaceuticals Inc.
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Table 5.3
Modified Body Mass Index (mBMI): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Genotype: V30M

Subgroup Visit	Vutrisiran (HELIOS-A) (N=54)	Patisiran (HELIOS-A) (N=20)
Day 421		
Actual Value		
n	53	19
Mean (SD)	1037.2 (211.2)	1026.8 (207.7)
SE	29.0	47.7
Median	1020.3	1039.4
Min, Max	697, 1645	683, 1553
Change from baseline		
n	53	19
Mean (SD)	13.4 (80.1)	8.8 (57.6)
SE	11.0	13.2
Median	-1.6	2.6
Min, Max	-141, 190	-62, 160

mBMI value = albumin (g/L) x weight (kg) / height (m)^2; higher values indicate higher nutritional status. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Alnylam Pharmaceuticals Inc.
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Table 5.3
Modified Body Mass Index (mBMI): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Genotype: V30M

Subgroup Visit	Vutrisiran (HELIOS-A) (N=54)	Patisiran (HELIOS-A) (N=20)
Day 505		
Actual Value		
n	53	20
Mean (SD)	1056.3 (214.9)	1039.5 (239.9)
SE	29.5	53.6
Median	1036.4	1016.7
Min, Max	614, 1585	662, 1607
Change from baseline		
n	53	20
Mean (SD)	32.6 (87.7)	33.7 (83.8)
SE	12.1	18.7
Median	25.5	29.4
Min, Max	-102, 307	-138, 180

mBMI value = albumin (g/L) x weight (kg) / height (m)^2; higher values indicate higher nutritional status. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Alnylam Pharmaceuticals Inc.
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Table 5.3
Modified Body Mass Index (mBMI): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Genotype: V30M

Subgroup Visit	Vutrisiran (HELIOS-A) (N=54)	Patisiran (HELIOS-A) (N=20)
Month 18		
Actual Value		
n	52	20
Mean (SD)	1048.0 (197.6)	1028.9 (228.3)
SE	27.4	51.1
Median	1046.1	1017.5
Min, Max	652, 1552	652, 1579
Change from baseline		
n	52	20
Mean (SD)	20.3 (90.8)	23.1 (88.8)
SE	12.6	19.9
Median	13.0	27.2
Min, Max	-150, 201	-143, 179

mBMI value = albumin (g/L) x weight (kg) / height (m)^2; higher values indicate higher nutritional status. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Alnylam Pharmaceuticals Inc.
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Table 5.3
Modified Body Mass Index (mBMI): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Genotype: non-V30M

Subgroup Visit	Vutrisiran (HELIOS-A) (N=68)	Patisiran (HELIOS-A) (N=22)
Baseline		
n	68	22
Mean (SD)	1081.9 (250.3)	1105.6 (225.1)
SE	30.4	48.0
Median	1071.6	1039.0
Min, Max	634, 1723	795, 1636
Day 85		
Actual Value		
n	63	20
Mean (SD)	1080.4 (245.7)	1088.1 (215.5)
SE	31.0	48.2
Median	1024.9	1041.7
Min, Max	667, 1750	801, 1569
Change from baseline		
n	63	20
Mean (SD)	-7.1 (77.0)	-20.0 (73.1)
SE	9.7	16.3
Median	2.7	-18.1
Min, Max	-295, 148	-183, 108

mBMI value = albumin (g/L) x weight (kg) / height (m)^2; higher values indicate higher nutritional status. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 5.3
Modified Body Mass Index (mBMI): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Genotype: non-V30M

Subgroup Visit	Vutrisiran (HELIOS-A) (N=68)	Patisiran (HELIOS-A) (N=22)
Day 169		
Actual Value		
n	65	20
Mean (SD)	1089.8 (247.4)	1098.5 (232.5)
SE	30.7	52.0
Median	1054.2	1055.0
Min, Max	599, 1778	707, 1578
Change from baseline		
n	65	20
Mean (SD)	5.3 (70.8)	-9.2 (83.3)
SE	8.8	18.6
Median	13.5	-26.4
Min, Max	-175, 191	-168, 132

mBMI value = albumin (g/L) x weight (kg) / height (m)^2; higher values indicate higher nutritional status. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 5.3
Modified Body Mass Index (mBMI): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Genotype: non-V30M

Subgroup Visit	Vutrisiran (HELIOS-A) (N=68)	Patisiran (HELIOS-A) (N=22)
Month 9		
Actual Value		
n	63	19
Mean (SD)	1099.0 (247.2)	1110.9 (275.4)
SE	31.1	63.2
Median	1072.9	1061.7
Min, Max	587, 1747	654, 1634
Change from baseline		
n	63	19
Mean (SD)	7.3 (68.7)	-13.4 (116.3)
SE	8.7	26.7
Median	11.7	5.2
Min, Max	-218, 145	-369, 141

mBMI value = albumin (g/L) x weight (kg) / height (m)^2; higher values indicate higher nutritional status. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 5.3
Modified Body Mass Index (mBMI): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Genotype: non-V30M

Subgroup Visit	Vutrisiran (HELIOS-A) (N=68)	Patisiran (HELIOS-A) (N=22)
Day 337		
Actual Value		
n	65	20
Mean (SD)	1099.8 (242.1)	1059.3 (237.3)
SE	30.0	53.1
Median	1073.7	1027.5
Min, Max	669, 1812	705, 1584
Change from baseline		
n	65	20
Mean (SD)	9.6 (79.4)	-48.5 (104.3)
SE	9.9	23.3
Median	13.5	-50.8
Min, Max	-162, 182	-317, 131

mBMI value = albumin (g/L) x weight (kg) / height (m)^2; higher values indicate higher nutritional status. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 5.3
Modified Body Mass Index (mBMI): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Genotype: non-V30M

Subgroup Visit	Vutrisiran (HELIOS-A) (N=68)	Patisiran (HELIOS-A) (N=22)
Day 421		
Actual Value		
n	65	18
Mean (SD)	1124.5 (262.5)	1061.1 (279.2)
SE	32.6	65.8
Median	1119.3	1024.6
Min, Max	660, 1877	635, 1557
Change from baseline		
n	65	18
Mean (SD)	29.7 (99.7)	-31.6 (116.5)
SE	12.4	27.5
Median	37.4	-13.7
Min, Max	-166, 228	-388, 93

mBMI value = albumin (g/L) x weight (kg) / height (m)^2; higher values indicate higher nutritional status. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 5.3
Modified Body Mass Index (mBMI): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Genotype: non-V30M

Subgroup Visit	Vutrisiran (HELIOS-A) (N=68)	Patisiran (HELIOS-A) (N=22)
Day 505		
Actual Value		
n	64	17
Mean (SD)	1109.7 (260.2)	1057.4 (250.5)
SE	32.5	60.8
Median	1101.1	993.5
Min, Max	598, 1858	732, 1558
Change from baseline		
n	64	17
Mean (SD)	16.6 (104.9)	-48.0 (96.9)
SE	13.1	23.5
Median	20.7	-55.6
Min, Max	-236, 249	-290, 187

mBMI value = albumin (g/L) x weight (kg) / height (m)^2; higher values indicate higher nutritional status. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 5.3
Modified Body Mass Index (mBMI): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Genotype: non-V30M

Subgroup Visit	Vutrisiran (HELIOS-A) (N=68)	Patisiran (HELIOS-A) (N=22)
Month 18		
Actual Value		
n	63	18
Mean (SD)	1115.9 (272.2)	1081.6 (250.2)
SE	34.3	59.0
Median	1087.1	1007.6
Min, Max	572, 2120	739, 1593
Change from baseline		
n	63	18
Mean (SD)	25.2 (110.6)	-11.0 (94.2)
SE	13.9	22.2
Median	30.9	-17.6
Min, Max	-216, 397	-284, 166

mBMI value = albumin (g/L) x weight (kg) / height (m)^2; higher values indicate higher nutritional status. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 5.3
Modified Body Mass Index (mBMI): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

FAP Stage: I

Subgroup Visit	Vutrisiran (HELIOS-A) (N=84)	Patisiran (HELIOS-A) (N=31)
Baseline		
n	84	31
Mean (SD)	1080.3 (234.3)	1068.4 (221.9)
SE	25.6	39.9
Median	1061.6	1027.6
Min, Max	589, 1723	646, 1636
Day 85		
Actual Value		
n	82	28
Mean (SD)	1085.2 (228.6)	1042.2 (219.7)
SE	25.2	41.5
Median	1031.6	1026.8
Min, Max	667, 1750	590, 1569
Change from baseline		
n	82	28
Mean (SD)	4.7 (72.6)	-25.0 (70.2)
SE	8.0	13.3
Median	6.3	-31.9
Min, Max	-190, 180	-183, 83

mBMI value = albumin (g/L) x weight (kg) / height (m)^2; higher values indicate higher nutritional status. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 5.3
Modified Body Mass Index (mBMI): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

FAP Stage: I

Subgroup Visit	Vutrisiran (HELIOS-A) (N=84)	Patisiran (HELIOS-A) (N=31)
Day 169		
Actual Value		
n	83	30
Mean (SD)	1079.6 (232.3)	1031.9 (221.8)
SE	25.5	40.5
Median	1054.2	1014.4
Min, Max	599, 1778	583, 1578
Change from baseline		
n	83	30
Mean (SD)	2.7 (74.3)	-34.2 (64.3)
SE	8.2	11.7
Median	0.0	-42.0
Min, Max	-159, 221	-168, 132

mBMI value = albumin (g/L) x weight (kg) / height (m)^2; higher values indicate higher nutritional status. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

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Table 5.3
Modified Body Mass Index (mBMI): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

FAP Stage: I

Subgroup Visit	Vutrisiran (HELIOS-A) (N=84)	Patisiran (HELIOS-A) (N=31)
Month 9		
Actual Value		
n	81	29
Mean (SD)	1089.6 (236.5)	1064.9 (265.2)
SE	26.3	49.2
Median	1070.5	1054.3
Min, Max	649, 1747	584, 1634
Change from baseline		
n	81	29
Mean (SD)	4.9 (70.0)	-11.3 (114.7)
SE	7.8	21.3
Median	-5.2	-21.2
Min, Max	-177, 174	-369, 169

mBMI value = albumin (g/L) x weight (kg) / height (m)^2; higher values indicate higher nutritional status. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

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Table 5.3
Modified Body Mass Index (mBMI): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

FAP Stage: I

Subgroup Visit	Vutrisiran (HELIOS-A) (N=84)	Patisiran (HELIOS-A) (N=31)
Day 337		
Actual Value		
n	80	30
Mean (SD)	1093.2 (230.6)	1028.1 (231.6)
SE	25.8	42.3
Median	1069.3	1021.4
Min, Max	705, 1812	601, 1584
Change from baseline		
n	80	30
Mean (SD)	10.4 (68.5)	-38.0 (90.2)
SE	7.7	16.5
Median	12.9	-46.9
Min, Max	-153, 142	-317, 131

mBMI value = albumin (g/L) x weight (kg) / height (m)^2; higher values indicate higher nutritional status. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 5.3
Modified Body Mass Index (mBMI): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

FAP Stage: I

Subgroup Visit	Vutrisiran (HELIOS-A) (N=84)	Patisiran (HELIOS-A) (N=31)
Day 421		
Actual Value		
n	83	29
Mean (SD)	1111.5 (244.0)	1051.7 (243.3)
SE	26.8	45.2
Median	1083.5	1049.1
Min, Max	703, 1877	635, 1557
Change from baseline		
n	83	29
Mean (SD)	26.5 (85.1)	-24.4 (94.4)
SE	9.3	17.5
Median	15.9	-12.5
Min, Max	-145, 215	-388, 95

mBMI value = albumin (g/L) x weight (kg) / height (m)^2; higher values indicate higher nutritional status. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 5.3
Modified Body Mass Index (mBMI): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

FAP Stage: I

Subgroup Visit	Vutrisiran (HELIOS-A) (N=84)	Patisiran (HELIOS-A) (N=31)
Day 505		
Actual Value		
n	82	29
Mean (SD)	1112.8 (239.6)	1057.5 (234.8)
SE	26.5	43.6
Median	1096.3	998.0
Min, Max	702, 1858	662, 1558
Change from baseline		
n	82	29
Mean (SD)	26.5 (89.8)	-15.1 (103.0)
SE	9.9	19.1
Median	35.7	-42.7
Min, Max	-236, 249	-290, 187

mBMI value = albumin (g/L) x weight (kg) / height (m)^2; higher values indicate higher nutritional status. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 5.3
Modified Body Mass Index (mBMI): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

FAP Stage: I

Subgroup Visit	Vutrisiran (HELIOS-A) (N=84)	Patisiran (HELIOS-A) (N=31)
Month 18		
Actual Value		
n	81	30
Mean (SD)	1109.9 (247.0)	1063.1 (238.0)
SE	27.4	43.5
Median	1057.7	1051.4
Min, Max	652, 2120	652, 1593
Change from baseline		
n	81	30
Mean (SD)	26.8 (98.3)	-3.0 (96.5)
SE	10.9	17.6
Median	20.2	-14.0
Min, Max	-187, 397	-284, 179

mBMI value = albumin (g/L) x weight (kg) / height (m)^2; higher values indicate higher nutritional status. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 5.3
Modified Body Mass Index (mBMI): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

FAP Stage: II&III

Subgroup Visit	Vutrisiran (HELIOS-A) (N=38)	Patisiran (HELIOS-A) (N=11)
Baseline		
n	38	11
Mean (SD)	1006.7 (227.5)	1029.1 (256.2)
SE	36.9	77.2
Median	1024.9	1030.6
Min, Max	634, 1455	658, 1534
Day 85		
Actual Value		
n	33	11
Mean (SD)	999.4 (195.6)	1046.3 (262.8)
SE	34.0	79.2
Median	1020.3	1041.4
Min, Max	669, 1407	714, 1570
Change from baseline		
n	33	11
Mean (SD)	-11.1 (81.5)	17.2 (62.7)
SE	14.2	18.9
Median	0.0	30.5
Min, Max	-295, 120	-111, 108

mBMI value = albumin (g/L) x weight (kg) / height (m)^2; higher values indicate higher nutritional status. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 5.3
Modified Body Mass Index (mBMI): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

FAP Stage: II&III

Subgroup Visit	Vutrisiran (HELIOS-A) (N=38)	Patisiran (HELIOS-A) (N=11)
Day 169		
Actual Value		
n	35	8
Mean (SD)	1021.4 (224.4)	1118.1 (251.1)
SE	37.9	88.8
Median	1020.1	1079.5
Min, Max	615, 1493	769, 1484
Change from baseline		
n	35	8
Mean (SD)	11.1 (71.4)	55.7 (69.3)
SE	12.1	24.5
Median	9.1	83.7
Min, Max	-175, 186	-50, 129

mBMI value = albumin (g/L) x weight (kg) / height (m)^2; higher values indicate higher nutritional status. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 5.3
Modified Body Mass Index (mBMI): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

FAP Stage: II&III

Subgroup Visit	Vutrisiran (HELIOS-A) (N=38)	Patisiran (HELIOS-A) (N=11)
Month 9		
Actual Value		
n	33	9
Mean (SD)	997.1 (223.7)	1073.4 (279.0)
SE	38.9	93.0
Median	958.8	1061.7
Min, Max	587, 1550	726, 1633
Change from baseline		
n	33	9
Mean (SD)	-2.3 (84.6)	18.5 (51.7)
SE	14.7	17.2
Median	-5.8	20.7
Min, Max	-218, 198	-57, 100

mBMI value = albumin (g/L) x weight (kg) / height (m)^2; higher values indicate higher nutritional status. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 5.3
Modified Body Mass Index (mBMI): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

FAP Stage: II&III

Subgroup Visit	Vutrisiran (HELIOS-A) (N=38)	Patisiran (HELIOS-A) (N=11)
Day 337		
Actual Value		
n	36	10
Mean (SD)	1027.2 (220.4)	1051.1 (221.5)
SE	36.7	70.0
Median	1018.3	997.7
Min, Max	669, 1552	781, 1547
Change from baseline		
n	36	10
Mean (SD)	17.1 (86.2)	22.2 (87.1)
SE	14.4	27.5
Median	14.4	23.8
Min, Max	-162, 190	-187, 123

mBMI value = albumin (g/L) x weight (kg) / height (m)^2; higher values indicate higher nutritional status. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 5.3
Modified Body Mass Index (mBMI): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

FAP Stage: II&III

Subgroup Visit	Vutrisiran (HELIOS-A) (N=38)	Patisiran (HELIOS-A) (N=11)
Day 421		
Actual Value		
n	35	8
Mean (SD)	1023.1 (235.1)	1013.5 (252.7)
SE	39.7	89.4
Median	974.9	907.5
Min, Max	660, 1645	780, 1553
Change from baseline		
n	35	8
Mean (SD)	12.7 (105.7)	38.3 (66.7)
SE	17.9	23.6
Median	-4.0	25.9
Min, Max	-166, 228	-46, 160

mBMI value = albumin (g/L) x weight (kg) / height (m)^2; higher values indicate higher nutritional status. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 5.3
Modified Body Mass Index (mBMI): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

FAP Stage: II&III

Subgroup Visit	Vutrisiran (HELIOS-A) (N=38)	Patisiran (HELIOS-A) (N=11)
Day 505		
Actual Value		
n	35	8
Mean (SD)	1021.6 (235.9)	1012.2 (278.9)
SE	39.9	98.6
Median	1030.9	975.7
Min, Max	598, 1585	683, 1607
Change from baseline		
n	35	8
Mean (SD)	17.5 (114.5)	37.0 (66.8)
SE	19.4	23.6
Median	12.7	14.7
Min, Max	-194, 307	-41, 170

mBMI value = albumin (g/L) x weight (kg) / height (m)^2; higher values indicate higher nutritional status. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 5.3
Modified Body Mass Index (mBMI): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

FAP Stage: II&III

Subgroup Visit	Vutrisiran (HELIOS-A) (N=38)	Patisiran (HELIOS-A) (N=11)
Month 18		
Actual Value		
n	34	8
Mean (SD)	1026.4 (225.0)	1019.2 (246.6)
SE	38.6	87.2
Median	999.3	985.7
Min, Max	572, 1446	766, 1579
Change from baseline		
n	34	8
Mean (SD)	14.0 (110.6)	44.0 (63.5)
SE	19.0	22.4
Median	22.1	49.4
Min, Max	-216, 203	-60, 124

mBMI value = albumin (g/L) x weight (kg) / height (m)^2; higher values indicate higher nutritional status. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 5.3
Modified Body Mass Index (mBMI): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Cardiac Subpopulation: Yes

Subgroup Visit	Vutrisiran (HELIOS-A) (N=40)	Patisiran (HELIOS-A) (N=14)
Baseline		
n	40	14
Mean (SD)	999.8 (251.9)	1014.4 (128.1)
SE	39.8	34.2
Median	954.6	1039.0
Min, Max	634, 1667	795, 1250
Day 85		
Actual Value		
n	37	13
Mean (SD)	990.0 (221.1)	1026.4 (155.0)
SE	36.4	43.0
Median	936.9	1037.1
Min, Max	667, 1551	801, 1305
Change from baseline		
n	37	13
Mean (SD)	-18.2 (80.8)	12.6 (50.3)
SE	13.3	13.9
Median	-9.9	8.3
Min, Max	-295, 120	-62, 108

mBMI value = albumin (g/L) x weight (kg) / height (m)^2; higher values indicate higher nutritional status. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 5.3
Modified Body Mass Index (mBMI): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Cardiac Subpopulation: Yes

Subgroup Visit	Vutrisiran (HELIOS-A) (N=40)	Patisiran (HELIOS-A) (N=14)
Day 169		
Actual Value		
n	39	13
Mean (SD)	1000.6 (242.5)	1034.2 (125.5)
SE	38.8	34.8
Median	986.1	1043.3
Min, Max	599, 1573	816, 1250
Change from baseline		
n	39	13
Mean (SD)	-6.3 (67.5)	8.3 (76.6)
SE	10.8	21.2
Median	0.0	0.0
Min, Max	-175, 138	-109, 129

mBMI value = albumin (g/L) x weight (kg) / height (m)^2; higher values indicate higher nutritional status. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 5.3
Modified Body Mass Index (mBMI): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Cardiac Subpopulation: Yes

Subgroup Visit	Vutrisiran (HELIOS-A) (N=40)	Patisiran (HELIOS-A) (N=14)
Month 9		
Actual Value		
n	38	13
Mean (SD)	1003.2 (248.8)	1021.4 (172.1)
SE	40.4	47.7
Median	948.7	1061.7
Min, Max	587, 1658	654, 1368
Change from baseline		
n	38	13
Mean (SD)	-12.1 (71.8)	-9.9 (120.3)
SE	11.6	33.4
Median	-14.6	12.8
Min, Max	-218, 112	-369, 118

mBMI value = albumin (g/L) x weight (kg) / height (m)^2; higher values indicate higher nutritional status. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 5.3
Modified Body Mass Index (mBMI): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Cardiac Subpopulation: Yes

Subgroup Visit	Vutrisiran (HELIOS-A) (N=40)	Patisiran (HELIOS-A) (N=14)
Day 337		
Actual Value		
n	38	14
Mean (SD)	1005.4 (232.3)	993.8 (157.2)
SE	37.7	42.0
Median	948.6	991.4
Min, Max	669, 1552	705, 1233
Change from baseline		
n	38	14
Mean (SD)	-9.9 (74.8)	-20.7 (115.7)
SE	12.1	30.9
Median	-10.3	1.6
Min, Max	-162, 182	-317, 131

mBMI value = albumin (g/L) x weight (kg) / height (m)^2; higher values indicate higher nutritional status. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 5.3
Modified Body Mass Index (mBMI): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Cardiac Subpopulation: Yes

Subgroup Visit	Vutrisiran (HELIOS-A) (N=40)	Patisiran (HELIOS-A) (N=14)
Day 421		
Actual Value		
n	38	13
Mean (SD)	1022.1 (253.9)	980.2 (183.3)
SE	41.2	50.8
Median	935.1	1049.1
Min, Max	660, 1645	635, 1287
Change from baseline		
n	38	13
Mean (SD)	6.8 (98.3)	-31.0 (128.0)
SE	16.0	35.5
Median	-9.3	-12.5
Min, Max	-166, 228	-388, 93

mBMI value = albumin (g/L) x weight (kg) / height (m)^2; higher values indicate higher nutritional status. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 5.3
Modified Body Mass Index (mBMI): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Cardiac Subpopulation: Yes

Subgroup Visit	Vutrisiran (HELIOS-A) (N=40)	Patisiran (HELIOS-A) (N=14)
Day 505		
Actual Value		
n	37	13
Mean (SD)	999.0 (250.1)	1014.6 (188.9)
SE	41.1	52.4
Median	951.6	1035.3
Min, Max	598, 1585	732, 1314
Change from baseline		
n	37	13
Mean (SD)	-17.0 (102.1)	3.4 (129.1)
SE	16.8	35.8
Median	-35.9	4.3
Min, Max	-236, 242	-290, 187

mBMI value = albumin (g/L) x weight (kg) / height (m)^2; higher values indicate higher nutritional status. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 5.3
Modified Body Mass Index (mBMI): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Cardiac Subpopulation: Yes

Subgroup Visit	Vutrisiran (HELIOS-A) (N=40)	Patisiran (HELIOS-A) (N=14)
Month 18		
Actual Value		
n	37	13
Mean (SD)	1017.8 (258.4)	1012.2 (152.6)
SE	42.5	42.3
Median	954.4	1019.4
Min, Max	572, 1693	739, 1242
Change from baseline		
n	37	13
Mean (SD)	-5.4 (90.4)	1.0 (105.1)
SE	14.9	29.2
Median	-8.8	28.1
Min, Max	-216, 201	-284, 124

mBMI value = albumin (g/L) x weight (kg) / height (m)^2; higher values indicate higher nutritional status. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

Alnylam Pharmaceuticals Inc.
ALN-TTRSC02-002

Table 5.3
Modified Body Mass Index (mBMI): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Cardiac Subpopulation: No

Subgroup Visit	Vutrisiran (HELIOS-A) (N=82)	Patisiran (HELIOS-A) (N=28)
Baseline		
n	82	28
Mean (SD)	1085.5 (220.6)	1080.0 (264.7)
SE	24.4	50.0
Median	1070.6	1025.4
Min, Max	589, 1723	646, 1636
Day 85		
Actual Value		
n	78	26
Mean (SD)	1094.0 (216.2)	1051.9 (260.7)
SE	24.5	51.1
Median	1067.6	1026.6
Min, Max	717, 1750	590, 1570
Change from baseline		
n	78	26
Mean (SD)	8.9 (71.3)	-25.9 (75.7)
SE	8.1	14.8
Median	11.0	-31.9
Min, Max	-164, 180	-183, 97

mBMI value = albumin (g/L) x weight (kg) / height (m)^2; higher values indicate higher nutritional status. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

Alnylam Pharmaceuticals Inc.
ALN-TTRSC02-002

Table 5.3
Modified Body Mass Index (mBMI): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Cardiac Subpopulation: No

Subgroup Visit	Vutrisiran (HELIOS-A) (N=82)	Patisiran (HELIOS-A) (N=28)
Day 169		
Actual Value		
n	79	25
Mean (SD)	1092.9 (219.6)	1058.3 (267.8)
SE	24.7	53.6
Median	1081.1	1038.1
Min, Max	692, 1778	583, 1578
Change from baseline		
n	79	25
Mean (SD)	10.8 (75.7)	-27.5 (71.7)
SE	8.5	14.3
Median	13.5	-47.9
Min, Max	-159, 221	-168, 132

mBMI value = albumin (g/L) x weight (kg) / height (m)^2; higher values indicate higher nutritional status. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

Alnylam Pharmaceuticals Inc.
ALN-TTRSC02-002

Table 5.3
Modified Body Mass Index (mBMI): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Cardiac Subpopulation: No

Subgroup Visit	Vutrisiran (HELIOS-A) (N=82)	Patisiran (HELIOS-A) (N=28)
Month 9		
Actual Value		
n	76	25
Mean (SD)	1092.6 (224.7)	1090.5 (302.5)
SE	25.8	60.5
Median	1073.5	1053.3
Min, Max	649, 1747	584, 1634
Change from baseline		
n	76	25
Mean (SD)	10.3 (74.8)	-1.3 (96.1)
SE	8.6	19.2
Median	17.4	-36.3
Min, Max	-177, 198	-145, 169

mBMI value = albumin (g/L) x weight (kg) / height (m)^2; higher values indicate higher nutritional status. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

Alnylam Pharmaceuticals Inc.
ALN-TTRSC02-002

Table 5.3
Modified Body Mass Index (mBMI): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Cardiac Subpopulation: No

Subgroup Visit	Vutrisiran (HELIOS-A) (N=82)	Patisiran (HELIOS-A) (N=28)
Day 337		
Actual Value		
n	78	26
Mean (SD)	1105.5 (221.0)	1055.4 (256.5)
SE	25.0	50.3
Median	1085.2	1041.0
Min, Max	705, 1812	601, 1584
Change from baseline		
n	78	26
Mean (SD)	23.3 (71.7)	-24.2 (79.4)
SE	8.1	15.6
Median	22.3	-36.1
Min, Max	-162, 190	-187, 123

mBMI value = albumin (g/L) x weight (kg) / height (m)^2; higher values indicate higher nutritional status. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

Alnylam Pharmaceuticals Inc.
ALN-TTRSC02-002

Table 5.3
Modified Body Mass Index (mBMI): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Cardiac Subpopulation: No

Subgroup Visit	Vutrisiran (HELIOS-A) (N=82)	Patisiran (HELIOS-A) (N=28)
Day 421		
Actual Value		
n	80	24
Mean (SD)	1115.3 (234.5)	1077.8 (266.2)
SE	26.2	54.3
Median	1101.5	1022.5
Min, Max	697, 1877	683, 1557
Change from baseline		
n	80	24
Mean (SD)	29.8 (87.6)	0.1 (66.2)
SE	9.8	13.5
Median	19.1	-4.7
Min, Max	-145, 215	-162, 160

mBMI value = albumin (g/L) x weight (kg) / height (m)^2; higher values indicate higher nutritional status. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

Alnylam Pharmaceuticals Inc.
ALN-TTRSC02-002

Table 5.3
Modified Body Mass Index (mBMI): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Cardiac Subpopulation: No

Subgroup Visit	Vutrisiran (HELIOS-A) (N=82)	Patisiran (HELIOS-A) (N=28)
Day 505		
Actual Value		
n	80	24
Mean (SD)	1125.5 (227.6)	1065.7 (267.9)
SE	25.4	54.7
Median	1136.6	983.9
Min, Max	701, 1858	662, 1607
Change from baseline		
n	80	24
Mean (SD)	42.7 (89.7)	-7.8 (79.2)
SE	10.0	16.2
Median	45.6	-17.9
Min, Max	-194, 307	-138, 180

mBMI value = albumin (g/L) x weight (kg) / height (m)^2; higher values indicate higher nutritional status. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

Alnylam Pharmaceuticals Inc.
ALN-TTRSC02-002

Table 5.3
Modified Body Mass Index (mBMI): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Cardiac Subpopulation: No

Subgroup Visit	Vutrisiran (HELIOS-A) (N=82)	Patisiran (HELIOS-A) (N=28)
Month 18		
Actual Value		
n	78	25
Mean (SD)	1117.2 (229.8)	1075.6 (271.4)
SE	26.0	54.3
Median	1120.0	1005.6
Min, Max	652, 2120	652, 1593
Change from baseline		
n	78	25
Mean (SD)	36.4 (104.6)	10.0 (86.3)
SE	11.8	17.3
Median	40.3	-10.3
Min, Max	-201, 397	-143, 179

mBMI value = albumin (g/L) x weight (kg) / height (m)^2; higher values indicate higher nutritional status. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

Alnylam Pharmaceuticals Inc.
ALN-TTRSC02-002

Table 5.3
Modified Body Mass Index (mBMI): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Weight (kg): <65

Subgroup Visit	Vutrisiran (HELIOS-A) (N=46)	Patisiran (HELIOS-A) (N=15)
Baseline		
n	46	15
Mean (SD)	852.4 (125.0)	873.8 (135.5)
SE	18.4	35.0
Median	833.5	875.8
Min, Max	589, 1162	646, 1078
Day 85		
Actual Value		
n	44	13
Mean (SD)	873.3 (109.1)	819.5 (98.4)
SE	16.4	27.3
Median	867.5	831.5
Min, Max	667, 1112	590, 990
Change from baseline		
n	44	13
Mean (SD)	17.3 (53.8)	-27.1 (65.8)
SE	8.1	18.3
Median	11.6	-35.6
Min, Max	-86, 148	-148, 63

mBMI value = albumin (g/L) x weight (kg) / height (m)^2; higher values indicate higher nutritional status. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

Alnylam Pharmaceuticals Inc.
ALN-TTRSC02-002

Table 5.3
Modified Body Mass Index (mBMI): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Weight (kg): <65

Subgroup Visit	Vutrisiran (HELIOS-A) (N=46)	Patisiran (HELIOS-A) (N=15)
Day 169		
Actual Value		
n	45	13
Mean (SD)	867.9 (117.4)	842.8 (137.7)
SE	17.5	38.2
Median	869.5	870.3
Min, Max	599, 1082	583, 1117
Change from baseline		
n	45	13
Mean (SD)	12.5 (64.6)	-27.7 (79.7)
SE	9.6	22.1
Median	9.1	-47.9
Min, Max	-152, 141	-168, 111

mBMI value = albumin (g/L) x weight (kg) / height (m)^2; higher values indicate higher nutritional status. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

Alnylam Pharmaceuticals Inc.
ALN-TTRSC02-002

Table 5.3
Modified Body Mass Index (mBMI): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Weight (kg): <65

Subgroup Visit	Vutrisiran (HELIOS-A) (N=46)	Patisiran (HELIOS-A) (N=15)
Month 9		
Actual Value		
n	44	14
Mean (SD)	859.0 (123.3)	839.3 (159.4)
SE	18.6	42.6
Median	834.0	837.9
Min, Max	587, 1189	584, 1247
Change from baseline		
n	44	14
Mean (SD)	-0.1 (62.5)	-41.6 (125.3)
SE	9.4	33.5
Median	-6.7	-41.8
Min, Max	-138, 112	-369, 169

mBMI value = albumin (g/L) x weight (kg) / height (m)^2; higher values indicate higher nutritional status. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

Alnylam Pharmaceuticals Inc.
ALN-TTRSC02-002

Table 5.3
Modified Body Mass Index (mBMI): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Weight (kg): <65

Subgroup Visit	Vutrisiran (HELIOS-A) (N=46)	Patisiran (HELIOS-A) (N=15)
Day 337		
Actual Value		
n	44	15
Mean (SD)	885.1 (118.2)	840.4 (136.4)
SE	17.8	35.2
Median	874.9	816.5
Min, Max	669, 1204	601, 1168
Change from baseline		
n	44	15
Mean (SD)	26.0 (63.4)	-33.4 (108.6)
SE	9.6	28.0
Median	28.4	-44.7
Min, Max	-103, 182	-317, 123

mBMI value = albumin (g/L) x weight (kg) / height (m)^2; higher values indicate higher nutritional status. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

Alnylam Pharmaceuticals Inc.
ALN-TTRSC02-002

Table 5.3
Modified Body Mass Index (mBMI): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Weight (kg): <65

Subgroup Visit	Vutrisiran (HELIOS-A) (N=46)	Patisiran (HELIOS-A) (N=15)
Day 421		
Actual Value		
n	44	14
Mean (SD)	881.0 (126.7)	851.0 (126.4)
SE	19.1	33.8
Median	868.5	842.5
Min, Max	660, 1200	635, 1113
Change from baseline		
n	44	14
Mean (SD)	21.9 (76.7)	-29.8 (125.8)
SE	11.6	33.6
Median	9.3	-14.4
Min, Max	-142, 228	-388, 160

mBMI value = albumin (g/L) x weight (kg) / height (m)^2; higher values indicate higher nutritional status. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

Alnylam Pharmaceuticals Inc.
ALN-TTRSC02-002

Table 5.3
Modified Body Mass Index (mBMI): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Weight (kg): <65

Subgroup Visit	Vutrisiran (HELIOS-A) (N=46)	Patisiran (HELIOS-A) (N=15)
Day 505		
Actual Value		
n	43	14
Mean (SD)	876.4 (135.5)	866.5 (160.6)
SE	20.7	42.9
Median	872.7	854.6
Min, Max	598, 1177	662, 1258
Change from baseline		
n	43	14
Mean (SD)	20.3 (75.2)	-7.1 (121.4)
SE	11.5	32.5
Median	16.6	4.0
Min, Max	-137, 182	-290, 180

mBMI value = albumin (g/L) x weight (kg) / height (m)^2; higher values indicate higher nutritional status. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

Alnylam Pharmaceuticals Inc.
ALN-TTRSC02-002

Table 5.3
Modified Body Mass Index (mBMI): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Weight (kg): <65

Subgroup Visit	Vutrisiran (HELIOS-A) (N=46)	Patisiran (HELIOS-A) (N=15)
Month 18		
Actual Value		
n	42	15
Mean (SD)	879.4 (125.5)	867.1 (147.5)
SE	19.4	38.1
Median	884.7	865.5
Min, Max	572, 1202	652, 1249
Change from baseline		
n	42	15
Mean (SD)	16.1 (71.8)	-6.6 (115.1)
SE	11.1	29.7
Median	17.4	-17.6
Min, Max	-139, 200	-284, 171

mBMI value = albumin (g/L) x weight (kg) / height (m)^2; higher values indicate higher nutritional status. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

Alnylam Pharmaceuticals Inc.
ALN-TTRSC02-002

Table 5.3
Modified Body Mass Index (mBMI): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Weight (kg): ≥65

Subgroup Visit	Vutrisiran (HELIOS-A) (N=76)	Patisiran (HELIOS-A) (N=27)
Baseline		
n	76	27
Mean (SD)	1181.4 (193.5)	1160.5 (205.3)
SE	22.2	39.5
Median	1139.8	1098.6
Min, Max	705, 1723	795, 1636
Day 85		
Actual Value		
n	71	26
Mean (SD)	1176.6 (193.5)	1155.3 (189.7)
SE	23.0	37.2
Median	1165.3	1101.9
Min, Max	766, 1750	825, 1570
Change from baseline		
n	71	26
Mean (SD)	-10.4 (84.5)	-6.1 (72.3)
SE	10.0	14.2
Median	-4.9	5.8
Min, Max	-295, 180	-183, 108

mBMI value = albumin (g/L) x weight (kg) / height (m)^2; higher values indicate higher nutritional status. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

Alnylam Pharmaceuticals Inc.
ALN-TTRSC02-002

Table 5.3
Modified Body Mass Index (mBMI): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Weight (kg): ≥65

Subgroup Visit	Vutrisiran (HELIOS-A) (N=76)	Patisiran (HELIOS-A) (N=27)
Day 169		
Actual Value		
n	73	25
Mean (SD)	1182.3 (199.4)	1157.9 (186.9)
SE	23.3	37.4
Median	1156.3	1081.2
Min, Max	692, 1778	880, 1578
Change from baseline		
n	73	25
Mean (SD)	0.6 (78.1)	-8.7 (72.3)
SE	9.1	14.5
Median	1.6	-24.0
Min, Max	-175, 221	-108, 132

mBMI value = albumin (g/L) x weight (kg) / height (m)^2; higher values indicate higher nutritional status. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

Alnylam Pharmaceuticals Inc.
ALN-TTRSC02-002

Table 5.3
Modified Body Mass Index (mBMI): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Weight (kg): ≥65

Subgroup Visit	Vutrisiran (HELIOS-A) (N=76)	Patisiran (HELIOS-A) (N=27)
Month 9		
Actual Value		
n	70	24
Mean (SD)	1190.9 (196.0)	1199.7 (220.0)
SE	23.4	44.9
Median	1198.3	1137.1
Min, Max	754, 1747	922, 1634
Change from baseline		
n	70	24
Mean (SD)	4.6 (81.1)	17.5 (83.7)
SE	9.7	17.1
Median	0.3	13.4
Min, Max	-218, 198	-129, 151

mBMI value = albumin (g/L) x weight (kg) / height (m)^2; higher values indicate higher nutritional status. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

Alnylam Pharmaceuticals Inc.
ALN-TTRSC02-002

Table 5.3
Modified Body Mass Index (mBMI): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Weight (kg): ≥65

Subgroup Visit	Vutrisiran (HELIOS-A) (N=76)	Patisiran (HELIOS-A) (N=27)
Day 337		
Actual Value		
n	72	25
Mean (SD)	1187.3 (202.6)	1149.9 (187.3)
SE	23.9	37.5
Median	1185.4	1092.8
Min, Max	773, 1812	880, 1584
Change from baseline		
n	72	25
Mean (SD)	4.2 (79.2)	-16.7 (82.7)
SE	9.3	16.5
Median	-4.7	-16.9
Min, Max	-162, 190	-187, 131

mBMI value = albumin (g/L) x weight (kg) / height (m)^2; higher values indicate higher nutritional status. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

Alnylam Pharmaceuticals Inc.
ALN-TTRSC02-002

Table 5.3
Modified Body Mass Index (mBMI): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Weight (kg): ≥65

Subgroup Visit	Vutrisiran (HELIOS-A) (N=76)	Patisiran (HELIOS-A) (N=27)
Day 421		
Actual Value		
n	74	23
Mean (SD)	1206.7 (213.7)	1160.6 (220.7)
SE	24.8	46.0
Median	1202.6	1122.2
Min, Max	770, 1877	780, 1557
Change from baseline		
n	74	23
Mean (SD)	22.7 (99.6)	0.7 (64.6)
SE	11.6	13.5
Median	18.0	-1.6
Min, Max	-166, 215	-162, 95

mBMI value = albumin (g/L) x weight (kg) / height (m)^2; higher values indicate higher nutritional status. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

Alnylam Pharmaceuticals Inc.
ALN-TTRSC02-002

Table 5.3
Modified Body Mass Index (mBMI): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Weight (kg): ≥65

Subgroup Visit	Vutrisiran (HELIOS-A) (N=76)	Patisiran (HELIOS-A) (N=27)
Day 505		
Actual Value		
n	74	23
Mean (SD)	1207.0 (202.9)	1158.0 (215.9)
SE	23.6	45.0
Median	1193.8	1140.0
Min, Max	817, 1858	794, 1607
Change from baseline		
n	74	23
Mean (SD)	25.9 (108.7)	-1.9 (83.5)
SE	12.6	17.4
Median	25.2	-5.1
Min, Max	-236, 307	-138, 187

mBMI value = albumin (g/L) x weight (kg) / height (m)^2; higher values indicate higher nutritional status. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

Alnylam Pharmaceuticals Inc.
ALN-TTRSC02-002

Table 5.3
Modified Body Mass Index (mBMI): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Weight (kg): ≥65

Subgroup Visit	Vutrisiran (HELIOS-A) (N=76)	Patisiran (HELIOS-A) (N=27)
Month 18		
Actual Value		
n	73	23
Mean (SD)	1203.6 (213.1)	1175.7 (203.6)
SE	24.9	42.5
Median	1188.0	1098.6
Min, Max	857, 2120	864, 1593
Change from baseline		
n	73	23
Mean (SD)	26.9 (115.8)	15.7 (74.4)
SE	13.6	15.5
Median	38.0	26.2
Min, Max	-216, 397	-108, 179

mBMI value = albumin (g/L) x weight (kg) / height (m)^2; higher values indicate higher nutritional status. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

Subgruppenanalysen zum Endpunkt „Veränderung der Mobilität gemessen anhand des T10MWT“

T10MWT (Kontinuierliche Analyse)

Alnylam Pharmaceuticals Inc.
ALN-TTRSC02-002

Table 4.3
10-meter Walk Test (10-MWT): Change from Baseline to Month 18, MMRM Model
Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A) Subgroup Analysis
mITT Population

Subgroup Visit	LS Mean (95% CI) Vutrisiran (HELIOS-A) (N=122)	LS Mean (95% CI) Patisiran (HELIOS-A) (N=42)	LS Mean Difference (Vutrisiran-Patisiran) (95% CI), p-value	Standardized Effect Size (95% CI)
Age (years)				
<65	75	30		
Month 9	0.02 (-0.02, 0.06)	-0.04 (-0.11, 0.03)	0.06 (-0.02, 0.14), 0.1584	0.32 (-0.10, 0.75)
Month 18	-0.00 (-0.06, 0.05)	-0.05 (-0.14, 0.04)	0.05 (-0.05, 0.16), 0.3346	0.20 (-0.23, 0.63)
≥65	43	10		
Month 9	-0.03 (-0.09, 0.03)	-0.04 (-0.15, 0.08)	0.01 (-0.12, 0.14), 0.9155	0.03 (-0.65, 0.71)
Month 18	-0.05 (-0.12, 0.02)	-0.05 (-0.18, 0.08)	0.00 (-0.14, 0.15), 0.9801	0.01 (-0.71, 0.72)
p-value of Treatment*Age	0.5118			

10-meter walk test speed (m/s) = 10 meters/mean time (seconds) taken to complete 2 assessments at each visit, imputed as 0 for patients unable to perform the walk; higher speeds indicate greater ambulatory function. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.
LS estimates and p-value derived from mixed-effects model for repeated measures (MMRM), controlling for categorical factors (treatment, visit), the subgroup variable, continuous covariate (baseline value), and interaction (treatment by visit, treatment by subgroup).
Standardized effect size (d) = LS mean difference/estimated pooled standard deviation with the small sample bias correction.

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Table 4.3
10-meter Walk Test (10-MWT): Change from Baseline to Month 18, MMRM Model
Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A) Subgroup Analysis
mITT Population

Subgroup Visit	LS Mean (95% CI) Vutrisiran (HELIOS-A) (N=122)	LS Mean (95% CI) Patisiran (HELIOS-A) (N=42)	LS Mean Difference (Vutrisiran-Patisiran) (95% CI), p-value	Standardized Effect Size (95% CI)
Sex				
Male	77	25		
Month 9	-0.01 (-0.05, 0.04)	-0.03 (-0.10, 0.05)	0.02 (-0.06, 0.11), 0.6210	0.11 (-0.34, 0.56)
Month 18	-0.03 (-0.08, 0.03)	-0.04 (-0.14, 0.05)	0.02 (-0.09, 0.13), 0.7730	0.06 (-0.41, 0.52)
Female	41	15		
Month 9	0.01 (-0.05, 0.07)	-0.06 (-0.15, 0.04)	0.07 (-0.04, 0.18), 0.2161	0.41 (-0.18, 1.00)
Month 18	-0.01 (-0.08, 0.06)	-0.07 (-0.19, 0.04)	0.06 (-0.07, 0.20), 0.3296	0.27 (-0.32, 0.85)
p-value of Treatment*Sex	0.4907			

10-meter walk test speed (m/s) = 10 meters/mean time (seconds) taken to complete 2 assessments at each visit, imputed as 0 for patients unable to perform the walk; higher speeds indicate greater ambulatory function. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.
LS estimates and p-value derived from mixed-effects model for repeated measures (MMRM), controlling for categorical factors (treatment, visit), the subgroup variable, continuous covariate (baseline value), and interaction (treatment by visit, treatment by subgroup).
Standardized effect size (d) = LS mean difference/estimated pooled standard deviation with the small sample bias correction.

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Table 4.3
10-meter Walk Test (10-MWT): Change from Baseline to Month 18, MMRM Model
Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A) Subgroup Analysis
mITT Population

Subgroup Visit	LS Mean (95% CI) Vutrisiran (HELIOS-A) (N=122)	LS Mean (95% CI) Patisiran (HELIOS-A) (N=42)	LS Mean Difference (Vutrisiran-Patisiran) (95% CI), p-value	Standardized Effect Size (95% CI)
Race				
White	83	28		
Month 9	-0.01 (-0.05, 0.03)	-0.04 (-0.11, 0.03)	0.03 (-0.05, 0.11), 0.5217	0.14 (-0.29, 0.57)
Month 18	-0.03 (-0.09, 0.02)	-0.06 (-0.15, 0.04)	0.02 (-0.09, 0.13), 0.6942	0.08 (-0.36, 0.51)
All Other Races	35	12		
Month 9	0.03 (-0.03, 0.10)	-0.04 (-0.14, 0.07)	0.07 (-0.05, 0.19), 0.2647	0.38 (-0.27, 1.03)
Month 18	0.01 (-0.06, 0.09)	-0.05 (-0.17, 0.07)	0.06 (-0.08, 0.21), 0.3673	0.27 (-0.40, 0.94)
p-value of Treatment*Race	0.5578			

10-meter walk test speed (m/s) = 10 meters/mean time (seconds) taken to complete 2 assessments at each visit, imputed as 0 for patients unable to perform the walk; higher speeds indicate greater ambulatory function. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.
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Standardized effect size (d) = LS mean difference/estimated pooled standard deviation with the small sample bias correction.

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Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A) Subgroup Analysis
mITT Population

Subgroup Visit	LS Mean (95% CI) Vutrisiran (HELIOS-A) (N=122)	LS Mean (95% CI) Patisiran (HELIOS-A) (N=42)	LS Mean Difference (Vutrisiran-Patisiran) (95% CI), p-value	Standardized Effect Size (95% CI)
Region				
North America	27	8		
Month 9	-0.03 (-0.10, 0.05)	-0.09 (-0.21, 0.04)	0.06 (-0.09, 0.21), 0.4149	0.25 (-0.53, 1.03)
Month 18	-0.05 (-0.13, 0.04)	-0.10 (-0.24, 0.04)	0.06 (-0.11, 0.22), 0.4919	0.15 (-0.67, 0.97)
Western Europe	39	18		
Month 9	-0.05 (-0.11, 0.01)	-0.02 (-0.11, 0.06)	-0.03 (-0.13, 0.08), 0.6020	-0.14 (-0.70, 0.41)
Month 18	-0.07 (-0.14, 0.00)	-0.04 (-0.14, 0.07)	-0.03 (-0.16, 0.09), 0.6219	-0.13 (-0.68, 0.42)
Rest of World	52	14		
Month 9	0.05 (-0.00, 0.10)	-0.04 (-0.13, 0.06)	0.08 (-0.02, 0.19), 0.1283	0.58 (-0.01, 1.18)
Month 18	0.03 (-0.04, 0.09)	-0.05 (-0.17, 0.06)	0.08 (-0.05, 0.21), 0.2239	0.36 (-0.24, 0.97)
p-value of Treatment*Region	0.3098			

10-meter walk test speed (m/s) = 10 meters/mean time (seconds) taken to complete 2 assessments at each visit, imputed as 0 for patients unable to perform the walk; higher speeds indicate greater ambulatory function. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.
LS estimates and p-value derived from mixed-effects model for repeated measures (MMRM), controlling for categorical factors (treatment, visit), the subgroup variable, continuous covariate (baseline value), and interaction (treatment by visit, treatment by subgroup).
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Table 4.3
10-meter Walk Test (10-MWT): Change from Baseline to Month 18, MMRM Model
Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A) Subgroup Analysis
mITT Population

Subgroup Visit	LS Mean (95% CI) Vutrisiran (HELIOS-A) (N=122)	LS Mean (95% CI) Patisiran (HELIOS-A) (N=42)	LS Mean Difference (Vutrisiran-Patisiran) (95% CI), p-value	Standardized Effect Size (95% CI)
Baseline NIS				
<50	77	27		
Month 9	0.02 (-0.02, 0.07)	-0.02 (-0.09, 0.05)	0.05 (-0.04, 0.13), 0.2679	0.23 (-0.21, 0.67)
Month 18	0.00 (-0.05, 0.06)	-0.04 (-0.13, 0.06)	0.04 (-0.07, 0.15), 0.4467	0.14 (-0.30, 0.58)
≥50	41	13		
Month 9	-0.04 (-0.11, 0.03)	-0.07 (-0.17, 0.04)	0.03 (-0.09, 0.14), 0.6695	0.16 (-0.46, 0.78)
Month 18	-0.06 (-0.14, 0.01)	-0.08 (-0.20, 0.04)	0.02 (-0.12, 0.16), 0.7655	0.12 (-0.52, 0.76)
p-value of Treatment*Baseline NIS	0.7719			

10-meter walk test speed (m/s) = 10 meters/mean time (seconds) taken to complete 2 assessments at each visit, imputed as 0 for patients unable to perform the walk; higher speeds indicate greater ambulatory function. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.
LS estimates and p-value derived from mixed-effects model for repeated measures (MMRM), controlling for categorical factors (treatment, visit), the subgroup variable, continuous covariate (baseline value), and interaction (treatment by visit, treatment by subgroup).
Standardized effect size (d) = LS mean difference/estimated pooled standard deviation with the small sample bias correction.

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Table 4.3
10-meter Walk Test (10-MWT): Change from Baseline to Month 18, MMRM Model
Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A) Subgroup Analysis
mITT Population

Subgroup Visit	LS Mean (95% CI) Vutrisiran (HELIOS-A) (N=122)	LS Mean (95% CI) Patisiran (HELIOS-A) (N=42)	LS Mean Difference (Vutrisiran-Patisiran) (95% CI), p-value	Standardized Effect Size (95% CI)
Previous Tetramer Stabilizer Use				
Yes	74	32		
Month 9	-0.00 (-0.05, 0.04)	-0.03 (-0.10, 0.03)	0.03 (-0.05, 0.11), 0.4585	0.17 (-0.25, 0.58)
Month 18	-0.02 (-0.08, 0.03)	-0.05 (-0.14, 0.04)	0.02 (-0.08, 0.13), 0.6443	0.09 (-0.33, 0.51)
No	44	8		
Month 9	0.01 (-0.05, 0.06)	-0.06 (-0.19, 0.07)	0.07 (-0.07, 0.21), 0.3293	0.33 (-0.42, 1.08)
Month 18	-0.01 (-0.08, 0.05)	-0.08 (-0.22, 0.06)	0.07 (-0.09, 0.22), 0.4160	0.25 (-0.54, 1.04)
p-value of Treatment*Previous Tetramer Stabilizer Use	0.6190			

10-meter walk test speed (m/s) = 10 meters/mean time (seconds) taken to complete 2 assessments at each visit, imputed as 0 for patients unable to perform the walk; higher speeds indicate greater ambulatory function. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.
LS estimates and p-value derived from mixed-effects model for repeated measures (MMRM), controlling for categorical factors (treatment, visit), the subgroup variable, continuous covariate (baseline value), and interaction (treatment by visit, treatment by subgroup).
Standardized effect size (d) = LS mean difference/estimated pooled standard deviation with the small sample bias correction.

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Table 4.3
10-meter Walk Test (10-MWT): Change from Baseline to Month 18, MMRM Model
Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A) Subgroup Analysis
mITT Population

Subgroup Visit	LS Mean (95% CI) Vutrisiran (HELIOS-A) (N=122)	LS Mean (95% CI) Patisiran (HELIOS-A) (N=42)	LS Mean Difference (Vutrisiran-Patisiran) (95% CI), p-value	Standardized Effect Size (95% CI)
Genotype				
V30M	53	20		
Month 9	0.00 (-0.05, 0.05)	-0.04 (-0.12, 0.04)	0.04 (-0.06, 0.14), 0.4130	0.19 (-0.32, 0.71)
Month 18	-0.02 (-0.08, 0.04)	-0.05 (-0.16, 0.05)	0.04 (-0.08, 0.15), 0.5586	0.14 (-0.37, 0.65)
non-V30M	65	20		
Month 9	-0.00 (-0.05, 0.05)	-0.04 (-0.12, 0.04)	0.04 (-0.06, 0.13), 0.4286	0.22 (-0.27, 0.72)
Month 18	-0.02 (-0.08, 0.04)	-0.05 (-0.16, 0.05)	0.03 (-0.08, 0.15), 0.5811	0.12 (-0.40, 0.64)
p-value of Treatment*Genotype	0.9721			

10-meter walk test speed (m/s) = 10 meters/mean time (seconds) taken to complete 2 assessments at each visit, imputed as 0 for patients unable to perform the walk; higher speeds indicate greater ambulatory function. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.
LS estimates and p-value derived from mixed-effects model for repeated measures (MMRM), controlling for categorical factors (treatment, visit), the subgroup variable, continuous covariate (baseline value), and interaction (treatment by visit, treatment by subgroup).
Standardized effect size (d) = LS mean difference/estimated pooled standard deviation with the small sample bias correction.

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10-meter Walk Test (10-MWT): Change from Baseline to Month 18, MMRM Model
Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A) Subgroup Analysis
mITT Population

Subgroup Visit	LS Mean (95% CI) Vutrisiran (HELIOS-A) (N=122)	LS Mean (95% CI) Patisiran (HELIOS-A) (N=42)	LS Mean Difference (Vutrisiran-Patisiran) (95% CI), p-value	Standardized Effect Size (95% CI)
FAP Stage				
I	83	30		
Month 9	0.04 (-0.00, 0.08)	0.00 (-0.07, 0.07)	0.04 (-0.04, 0.11), 0.3326	0.19 (-0.23, 0.61)
Month 18	0.02 (-0.04, 0.07)	-0.02 (-0.11, 0.07)	0.03 (-0.07, 0.14), 0.5223	0.12 (-0.30, 0.54)
II&III	35	10		
Month 9	-0.08 (-0.15, -0.01)	-0.14 (-0.26, -0.03)	0.06 (-0.07, 0.19), 0.3511	0.44 (-0.26, 1.14)
Month 18	-0.10 (-0.18, -0.03)	-0.16 (-0.29, -0.03)	0.06 (-0.09, 0.20), 0.4476	0.27 (-0.49, 1.03)
p-value of Treatment*FAP Stage	0.7605			

10-meter walk test speed (m/s) = 10 meters/mean time (seconds) taken to complete 2 assessments at each visit, imputed as 0 for patients unable to perform the walk; higher speeds indicate greater ambulatory function. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.
LS estimates and p-value derived from mixed-effects model for repeated measures (MMRM), controlling for categorical factors (treatment, visit), the subgroup variable, continuous covariate (baseline value), and interaction (treatment by visit, treatment by subgroup).
Standardized effect size (d) = LS mean difference/estimated pooled standard deviation with the small sample bias correction.

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Table 4.3
10-meter Walk Test (10-MWT): Change from Baseline to Month 18, MMRM Model
Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A) Subgroup Analysis
mITT Population

Subgroup Visit	LS Mean (95% CI) Vutrisiran (HELIOS-A) (N=122)	LS Mean (95% CI) Patisiran (HELIOS-A) (N=42)	LS Mean Difference (Vutrisiran-Patisiran) (95% CI), p-value	Standardized Effect Size (95% CI)
Cardiac Subpopulation				
Yes	38	14		
Month 9	-0.03 (-0.09, 0.03)	-0.00 (-0.10, 0.10)	-0.03 (-0.14, 0.09), 0.6371	-0.16 (-0.77, 0.44)
Month 18	-0.05 (-0.12, 0.02)	-0.02 (-0.13, 0.10)	-0.03 (-0.17, 0.10), 0.6339	-0.14 (-0.76, 0.48)
No	80	26		
Month 9	0.01 (-0.03, 0.06)	-0.06 (-0.13, 0.01)	0.07 (-0.01, 0.16), 0.0838	0.38 (-0.07, 0.82)
Month 18	-0.01 (-0.06, 0.05)	-0.07 (-0.17, 0.02)	0.07 (-0.04, 0.18), 0.2194	0.24 (-0.21, 0.69)
p-value of Treatment*Cardiac Subpopulation	0.1600			

10-meter walk test speed (m/s) = 10 meters/mean time (seconds) taken to complete 2 assessments at each visit, imputed as 0 for patients unable to perform the walk; higher speeds indicate greater ambulatory function. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.
LS estimates and p-value derived from mixed-effects model for repeated measures (MMRM), controlling for categorical factors (treatment, visit), the subgroup variable, continuous covariate (baseline value), and interaction (treatment by visit, treatment by subgroup).
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10-meter Walk Test (10-MWT): Change from Baseline to Month 18, MMRM Model
Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A) Subgroup Analysis
mITT Population

Subgroup Visit	LS Mean (95% CI) Vutrisiran (HELIOS-A) (N=122)	LS Mean (95% CI) Patisiran (HELIOS-A) (N=42)	LS Mean Difference (Vutrisiran-Patisiran) (95% CI), p-value	Standardized Effect Size (95% CI)
Weight (kg)				
<65	44	15		
Month 9	0.02 (-0.03, 0.08)	-0.06 (-0.16, 0.03)	0.08 (-0.03, 0.19), 0.1314	0.50 (-0.09, 1.08)
Month 18	0.00 (-0.06, 0.07)	-0.08 (-0.19, 0.03)	0.08 (-0.05, 0.21), 0.2290	0.33 (-0.25, 0.92)
≥65	74	25		
Month 9	-0.01 (-0.06, 0.03)	-0.02 (-0.10, 0.05)	0.01 (-0.07, 0.10), 0.7828	0.06 (-0.39, 0.51)
Month 18	-0.03 (-0.09, 0.02)	-0.04 (-0.13, 0.06)	0.01 (-0.10, 0.12), 0.9021	0.02 (-0.44, 0.49)
p-value of Treatment*Weight	0.3026			

10-meter walk test speed (m/s) = 10 meters/mean time (seconds) taken to complete 2 assessments at each visit, imputed as 0 for patients unable to perform the walk; higher speeds indicate greater ambulatory function. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.
LS estimates and p-value derived from mixed-effects model for repeated measures (MMRM), controlling for categorical factors (treatment, visit), the subgroup variable, continuous covariate (baseline value), and interaction (treatment by visit, treatment by subgroup).
Standardized effect size (d) = LS mean difference/estimated pooled standard deviation with the small sample bias correction.

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Table 4.5
10-meter Walk Test (10-MWT): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Age (years): <65

Subgroup Visit	Vutrisiran (HELIOS-A) (N=76)	Patisiran (HELIOS-A) (N=31)
Baseline		
n	76	31
Mean (SD)	1.065 (0.373)	1.019 (0.374)
SE	0.043	0.067
Median	1.090	1.000
Min, Max	0.22, 1.87	0.11, 1.58
Month 9		
Actual Value		
n	73	30
Mean (SD)	1.087 (0.429)	1.005 (0.401)
SE	0.050	0.073
Median	1.111	1.037
Min, Max	0.20, 2.32	0.00, 1.72
Change from baseline		
n	73	30
Mean (SD)	0.023 (0.170)	-0.038 (0.189)
SE	0.020	0.035
Median	0.008	-0.028
Min, Max	-0.41, 0.54	-0.50, 0.32

10-meter walk test speed (m/s) = 10 meters/mean time (seconds) taken to complete 2 assessments at each visit, imputed as 0 for patients unable to perform the walk; higher speeds indicate greater ambulatory function. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 4.5
10-meter Walk Test (10-MWT): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Age (years): <65

Subgroup Visit	Vutrisiran (HELIOS-A) (N=76)	Patisiran (HELIOS-A) (N=31)
Month 18		
Actual Value		
n	74	29
Mean (SD)	1.070 (0.434)	1.018 (0.481)
SE	0.050	0.089
Median	1.133	1.111
Min, Max	0.00, 1.84	0.00, 1.87
Change from baseline		
n	74	29
Mean (SD)	-0.008 (0.244)	-0.047 (0.293)
SE	0.028	0.054
Median	0.009	-0.029
Min, Max	-0.77, 0.44	-0.95, 0.45

10-meter walk test speed (m/s) = 10 meters/mean time (seconds) taken to complete 2 assessments at each visit, imputed as 0 for patients unable to perform the walk; higher speeds indicate greater ambulatory function. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 4.5
10-meter Walk Test (10-MWT): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Age (years): ≥65

Subgroup Visit	Vutrisiran (HELIOS-A) (N=46)	Patisiran (HELIOS-A) (N=11)
Baseline		
n	46	11
Mean (SD)	0.908 (0.410)	0.989 (0.486)
SE	0.060	0.147
Median	0.899	0.813
Min, Max	0.08, 1.66	0.46, 1.93
Month 9		
Actual Value		
n	42	10
Mean (SD)	0.909 (0.445)	0.971 (0.660)
SE	0.069	0.209
Median	0.906	0.747
Min, Max	0.09, 1.67	0.08, 2.31
Change from baseline		
n	42	10
Mean (SD)	-0.034 (0.201)	-0.036 (0.232)
SE	0.031	0.073
Median	-0.018	-0.052
Min, Max	-0.65, 0.42	-0.38, 0.38

10-meter walk test speed (m/s) = 10 meters/mean time (seconds) taken to complete 2 assessments at each visit, imputed as 0 for patients unable to perform the walk; higher speeds indicate greater ambulatory function. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 4.5
10-meter Walk Test (10-MWT): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Age (years): ≥65

Subgroup Visit	Vutrisiran (HELIOS-A) (N=46)	Patisiran (HELIOS-A) (N=11)
Month 18		
Actual Value		
n	39	9
Mean (SD)	0.919 (0.480)	0.970 (0.579)
SE	0.077	0.193
Median	0.874	0.833
Min, Max	0.00, 2.34	0.26, 2.19
Change from baseline		
n	39	9
Mean (SD)	-0.039 (0.291)	-0.032 (0.231)
SE	0.047	0.077
Median	-0.005	-0.048
Min, Max	-0.91, 0.72	-0.49, 0.26

10-meter walk test speed (m/s) = 10 meters/mean time (seconds) taken to complete 2 assessments at each visit, imputed as 0 for patients unable to perform the walk; higher speeds indicate greater ambulatory function. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 4.5
10-meter Walk Test (10-MWT): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Sex: Male

Subgroup Visit	Vutrisiran (HELIOS-A) (N=79)	Patisiran (HELIOS-A) (N=27)
Baseline		
n	79	27
Mean (SD)	1.031 (0.392)	1.021 (0.452)
SE	0.044	0.087
Median	1.053	1.000
Min, Max	0.08, 1.87	0.11, 1.93
Month 9		
Actual Value		
n	76	25
Mean (SD)	1.045 (0.458)	1.031 (0.492)
SE	0.053	0.098
Median	1.049	1.000
Min, Max	0.09, 2.32	0.07, 2.31
Change from baseline		
n	76	25
Mean (SD)	-0.002 (0.198)	-0.027 (0.191)
SE	0.023	0.038
Median	0.000	-0.036
Min, Max	-0.65, 0.54	-0.43, 0.38

10-meter walk test speed (m/s) = 10 meters/mean time (seconds) taken to complete 2 assessments at each visit, imputed as 0 for patients unable to perform the walk; higher speeds indicate greater ambulatory function. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Alnylam Pharmaceuticals Inc.
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Table 4.5
10-meter Walk Test (10-MWT): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Sex: Male

Subgroup Visit	Vutrisiran (HELIOS-A) (N=79)	Patisiran (HELIOS-A) (N=27)
Month 18		
Actual Value		
n	73	23
Mean (SD)	1.035 (0.471)	1.081 (0.476)
SE	0.055	0.099
Median	1.053	1.128
Min, Max	0.00, 2.34	0.08, 2.19
Change from baseline		
n	73	23
Mean (SD)	-0.034 (0.287)	-0.005 (0.238)
SE	0.034	0.050
Median	0.000	-0.029
Min, Max	-0.91, 0.72	-0.49, 0.45

10-meter walk test speed (m/s) = 10 meters/mean time (seconds) taken to complete 2 assessments at each visit, imputed as 0 for patients unable to perform the walk; higher speeds indicate greater ambulatory function. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Alnylam Pharmaceuticals Inc.
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Table 4.5
10-meter Walk Test (10-MWT): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Sex: Female

Subgroup Visit	Vutrisiran (HELIOS-A) (N=43)	Patisiran (HELIOS-A) (N=15)
Baseline		
n	43	15
Mean (SD)	0.959 (0.394)	0.993 (0.296)
SE	0.060	0.077
Median	1.037	1.000
Min, Max	0.20, 1.67	0.46, 1.54
Month 9		
Actual Value		
n	39	15
Mean (SD)	0.977 (0.408)	0.939 (0.439)
SE	0.065	0.113
Median	1.053	1.049
Min, Max	0.14, 1.60	0.00, 1.43
Change from baseline		
n	39	15
Mean (SD)	0.010 (0.152)	-0.054 (0.214)
SE	0.024	0.055
Median	0.000	-0.055
Min, Max	-0.30, 0.32	-0.50, 0.32

10-meter walk test speed (m/s) = 10 meters/mean time (seconds) taken to complete 2 assessments at each visit, imputed as 0 for patients unable to perform the walk; higher speeds indicate greater ambulatory function. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Alnylam Pharmaceuticals Inc.
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Table 4.5
10-meter Walk Test (10-MWT): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Sex: Female

Subgroup Visit	Vutrisiran (HELIOS-A) (N=43)	Patisiran (HELIOS-A) (N=15)
Month 18		
Actual Value		
n	40	15
Mean (SD)	0.986 (0.426)	0.892 (0.525)
SE	0.067	0.135
Median	1.053	0.910
Min, Max	0.12, 1.67	0.00, 1.87
Change from baseline		
n	40	15
Mean (SD)	0.009 (0.203)	-0.101 (0.326)
SE	0.032	0.084
Median	0.007	-0.103
Min, Max	-0.49, 0.43	-0.95, 0.43

10-meter walk test speed (m/s) = 10 meters/mean time (seconds) taken to complete 2 assessments at each visit, imputed as 0 for patients unable to perform the walk; higher speeds indicate greater ambulatory function. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Alnylam Pharmaceuticals Inc.
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Table 4.5
10-meter Walk Test (10-MWT): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Race: White

Subgroup Visit	Vutrisiran (HELIOS-A) (N=86)	Patisiran (HELIOS-A) (N=29)
Baseline		
n	86	29
Mean (SD)	1.051 (0.416)	1.012 (0.430)
SE	0.045	0.080
Median	1.108	0.952
Min, Max	0.08, 1.87	0.11, 1.93
Month 9		
Actual Value		
n	81	28
Mean (SD)	1.060 (0.454)	0.979 (0.534)
SE	0.050	0.101
Median	1.053	1.013
Min, Max	0.09, 2.32	0.00, 2.31
Change from baseline		
n	81	28
Mean (SD)	-0.010 (0.187)	-0.041 (0.193)
SE	0.021	0.036
Median	0.000	-0.039
Min, Max	-0.65, 0.45	-0.50, 0.38

10-meter walk test speed (m/s) = 10 meters/mean time (seconds) taken to complete 2 assessments at each visit, imputed as 0 for patients unable to perform the walk; higher speeds indicate greater ambulatory function. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Alnylam Pharmaceuticals Inc.
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Table 4.5
10-meter Walk Test (10-MWT): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Race: White

Subgroup Visit	Vutrisiran (HELIOS-A) (N=86)	Patisiran (HELIOS-A) (N=29)
Month 18		
Actual Value		
n	80	27
Mean (SD)	1.063 (0.450)	1.002 (0.578)
SE	0.050	0.111
Median	1.080	1.000
Min, Max	0.11, 2.34	0.00, 2.19
Change from baseline		
n	80	27
Mean (SD)	-0.029 (0.264)	-0.041 (0.308)
SE	0.029	0.059
Median	0.000	-0.029
Min, Max	-0.77, 0.72	-0.95, 0.45

10-meter walk test speed (m/s) = 10 meters/mean time (seconds) taken to complete 2 assessments at each visit, imputed as 0 for patients unable to perform the walk; higher speeds indicate greater ambulatory function. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Alnylam Pharmaceuticals Inc.
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Table 4.5
10-meter Walk Test (10-MWT): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Race: All Other Races

Subgroup Visit	Vutrisiran (HELIOS-A) (N=36)	Patisiran (HELIOS-A) (N=13)
Baseline		
n	36	13
Mean (SD)	0.897 (0.311)	1.008 (0.341)
SE	0.052	0.094
Median	0.931	1.053
Min, Max	0.22, 1.43	0.31, 1.54
Month 9		
Actual Value		
n	34	12
Mean (SD)	0.930 (0.399)	1.037 (0.282)
SE	0.068	0.081
Median	0.988	1.032
Min, Max	0.14, 1.60	0.49, 1.43
Change from baseline		
n	34	12
Mean (SD)	0.029 (0.173)	-0.029 (0.217)
SE	0.030	0.063
Median	0.065	-0.032
Min, Max	-0.40, 0.54	-0.43, 0.32

10-meter walk test speed (m/s) = 10 meters/mean time (seconds) taken to complete 2 assessments at each visit, imputed as 0 for patients unable to perform the walk; higher speeds indicate greater ambulatory function. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Alnylam Pharmaceuticals Inc.
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Table 4.5
10-meter Walk Test (10-MWT): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Race: All Other Races

Subgroup Visit	Vutrisiran (HELIOS-A) (N=36)	Patisiran (HELIOS-A) (N=13)
Month 18		
Actual Value		
n	33	11
Mean (SD)	0.907 (0.451)	1.018 (0.218)
SE	0.078	0.066
Median	0.939	1.128
Min, Max	0.00, 1.54	0.52, 1.28
Change from baseline		
n	33	11
Mean (SD)	0.007 (0.253)	-0.050 (0.190)
SE	0.044	0.057
Median	0.069	-0.093
Min, Max	-0.91, 0.43	-0.39, 0.25

10-meter walk test speed (m/s) = 10 meters/mean time (seconds) taken to complete 2 assessments at each visit, imputed as 0 for patients unable to perform the walk; higher speeds indicate greater ambulatory function. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 4.5
10-meter Walk Test (10-MWT): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Region: North America

Subgroup Visit	Vutrisiran (HELIOS-A) (N=27)	Patisiran (HELIOS-A) (N=8)
Baseline		
n	27	8
Mean (SD)	1.252 (0.261)	1.079 (0.290)
SE	0.050	0.103
Median	1.250	1.026
Min, Max	0.70, 1.67	0.61, 1.54
Month 9		
Actual Value		
n	25	8
Mean (SD)	1.278 (0.273)	0.985 (0.303)
SE	0.055	0.107
Median	1.333	1.037
Min, Max	0.51, 1.67	0.49, 1.43
Change from baseline		
n	25	8
Mean (SD)	-0.013 (0.249)	-0.093 (0.168)
SE	0.050	0.059
Median	0.000	-0.093
Min, Max	-0.65, 0.54	-0.36, 0.11

10-meter walk test speed (m/s) = 10 meters/mean time (seconds) taken to complete 2 assessments at each visit, imputed as 0 for patients unable to perform the walk; higher speeds indicate greater ambulatory function. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 4.5
10-meter Walk Test (10-MWT): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Region: North America

Subgroup Visit	Vutrisiran (HELIOS-A) (N=27)	Patisiran (HELIOS-A) (N=8)
Month 18		
Actual Value		
n	25	7
Mean (SD)	1.287 (0.433)	1.126 (0.673)
SE	0.087	0.254
Median	1.303	1.429
Min, Max	0.00, 2.34	0.00, 1.87
Change from baseline		
n	25	7
Mean (SD)	0.017 (0.342)	0.044 (0.481)
SE	0.068	0.182
Median	0.026	0.238
Min, Max	-0.91, 0.72	-0.95, 0.43

10-meter walk test speed (m/s) = 10 meters/mean time (seconds) taken to complete 2 assessments at each visit, imputed as 0 for patients unable to perform the walk; higher speeds indicate greater ambulatory function. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 4.5
10-meter Walk Test (10-MWT): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Region: Western Europe

Subgroup Visit	Vutrisiran (HELIOS-A) (N=42)	Patisiran (HELIOS-A) (N=20)
Baseline		
n	42	20
Mean (SD)	1.114 (0.404)	1.074 (0.416)
SE	0.062	0.093
Median	1.176	1.001
Min, Max	0.20, 1.87	0.31, 1.93
Month 9		
Actual Value		
n	38	18
Mean (SD)	1.120 (0.454)	1.122 (0.504)
SE	0.074	0.119
Median	1.082	1.056
Min, Max	0.19, 2.32	0.08, 2.31
Change from baseline		
n	38	18
Mean (SD)	-0.031 (0.195)	-0.009 (0.195)
SE	0.032	0.046
Median	-0.045	-0.024
Min, Max	-0.35, 0.45	-0.43, 0.38

10-meter walk test speed (m/s) = 10 meters/mean time (seconds) taken to complete 2 assessments at each visit, imputed as 0 for patients unable to perform the walk; higher speeds indicate greater ambulatory function. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Alnylam Pharmaceuticals Inc.
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Table 4.5
10-meter Walk Test (10-MWT): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Region: Western Europe

Subgroup Visit	Vutrisiran (HELIOS-A) (N=42)	Patisiran (HELIOS-A) (N=20)
Month 18		
Actual Value		
n	39	18
Mean (SD)	1.079 (0.371)	1.087 (0.462)
SE	0.059	0.109
Median	1.053	1.056
Min, Max	0.19, 1.84	0.26, 2.19
Change from baseline		
n	39	18
Mean (SD)	-0.083 (0.233)	-0.044 (0.217)
SE	0.037	0.051
Median	-0.117	-0.050
Min, Max	-0.64, 0.44	-0.49, 0.45

10-meter walk test speed (m/s) = 10 meters/mean time (seconds) taken to complete 2 assessments at each visit, imputed as 0 for patients unable to perform the walk; higher speeds indicate greater ambulatory function. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Alnylam Pharmaceuticals Inc.
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Table 4.5
10-meter Walk Test (10-MWT): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Region: Rest of World

Subgroup Visit	Vutrisiran (HELIOS-A) (N=53)	Patisiran (HELIOS-A) (N=14)
Baseline		
n	53	14
Mean (SD)	0.795 (0.332)	0.882 (0.423)
SE	0.046	0.113
Median	0.847	0.955
Min, Max	0.08, 1.44	0.11, 1.54
Month 9		
Actual Value		
n	52	14
Mean (SD)	0.827 (0.415)	0.841 (0.481)
SE	0.058	0.129
Median	0.906	0.952
Min, Max	0.09, 1.79	0.00, 1.43
Change from baseline		
n	52	14
Mean (SD)	0.033 (0.128)	-0.041 (0.221)
SE	0.018	0.059
Median	0.046	-0.028
Min, Max	-0.21, 0.35	-0.50, 0.32

10-meter walk test speed (m/s) = 10 meters/mean time (seconds) taken to complete 2 assessments at each visit, imputed as 0 for patients unable to perform the walk; higher speeds indicate greater ambulatory function. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Alnylam Pharmaceuticals Inc.
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Table 4.5
10-meter Walk Test (10-MWT): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Region: Rest of World

Subgroup Visit	Vutrisiran (HELIOS-A) (N=53)	Patisiran (HELIOS-A) (N=14)
Month 18		
Actual Value		
n	49	13
Mean (SD)	0.832 (0.450)	0.830 (0.429)
SE	0.064	0.119
Median	0.826	1.000
Min, Max	0.00, 1.77	0.07, 1.28
Change from baseline		
n	49	13
Mean (SD)	0.014 (0.226)	-0.089 (0.215)
SE	0.032	0.060
Median	0.051	-0.029
Min, Max	-0.77, 0.38	-0.43, 0.25

10-meter walk test speed (m/s) = 10 meters/mean time (seconds) taken to complete 2 assessments at each visit, imputed as 0 for patients unable to perform the walk; higher speeds indicate greater ambulatory function. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Alnylam Pharmaceuticals Inc.
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Table 4.5
10-meter Walk Test (10-MWT): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Baseline NIS: <50

Subgroup Visit	Vutrisiran (HELIOS-A) (N=78)	Patisiran (HELIOS-A) (N=27)
Baseline		
n	78	27
Mean (SD)	1.216 (0.276)	1.176 (0.328)
SE	0.031	0.063
Median	1.230	1.093
Min, Max	0.59, 1.87	0.59, 1.93
Month 9		
Actual Value		
n	76	27
Mean (SD)	1.239 (0.324)	1.151 (0.386)
SE	0.037	0.074
Median	1.201	1.111
Min, Max	0.51, 2.32	0.49, 2.31
Change from baseline		
n	76	27
Mean (SD)	0.023 (0.203)	-0.025 (0.193)
SE	0.023	0.037
Median	0.040	-0.015
Min, Max	-0.65, 0.54	-0.43, 0.38

10-meter walk test speed (m/s) = 10 meters/mean time (seconds) taken to complete 2 assessments at each visit, imputed as 0 for patients unable to perform the walk; higher speeds indicate greater ambulatory function. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 4.5
10-meter Walk Test (10-MWT): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Baseline NIS: <50

Subgroup Visit	Vutrisiran (HELIOS-A) (N=78)	Patisiran (HELIOS-A) (N=27)
Month 18		
Actual Value		
n	75	26
Mean (SD)	1.226 (0.352)	1.161 (0.472)
SE	0.041	0.093
Median	1.226	1.156
Min, Max	0.00, 2.34	0.00, 2.19
Change from baseline		
n	75	26
Mean (SD)	0.000 (0.294)	-0.020 (0.313)
SE	0.034	0.061
Median	0.026	-0.006
Min, Max	-0.91, 0.72	-0.95, 0.45

10-meter walk test speed (m/s) = 10 meters/mean time (seconds) taken to complete 2 assessments at each visit, imputed as 0 for patients unable to perform the walk; higher speeds indicate greater ambulatory function. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 4.5
10-meter Walk Test (10-MWT): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Baseline NIS: ≥50

Subgroup Visit	Vutrisiran (HELIOS-A) (N=44)	Patisiran (HELIOS-A) (N=15)
Baseline		
n	44	15
Mean (SD)	0.633 (0.275)	0.714 (0.348)
SE	0.041	0.090
Median	0.595	0.689
Min, Max	0.08, 1.13	0.11, 1.33
Month 9		
Actual Value		
n	39	13
Mean (SD)	0.598 (0.313)	0.676 (0.478)
SE	0.050	0.133
Median	0.645	0.800
Min, Max	0.09, 1.40	0.00, 1.43
Change from baseline		
n	39	13
Mean (SD)	-0.039 (0.130)	-0.061 (0.213)
SE	0.021	0.059
Median	-0.020	-0.043
Min, Max	-0.35, 0.27	-0.50, 0.32

10-meter walk test speed (m/s) = 10 meters/mean time (seconds) taken to complete 2 assessments at each visit, imputed as 0 for patients unable to perform the walk; higher speeds indicate greater ambulatory function. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 4.5
10-meter Walk Test (10-MWT): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Baseline NIS: ≥50

Subgroup Visit	Vutrisiran (HELIOS-A) (N=44)	Patisiran (HELIOS-A) (N=15)
Month 18		
Actual Value		
n	38	12
Mean (SD)	0.606 (0.337)	0.672 (0.386)
SE	0.055	0.111
Median	0.600	0.760
Min, Max	0.00, 1.42	0.07, 1.21
Change from baseline		
n	38	12
Mean (SD)	-0.056 (0.174)	-0.093 (0.172)
SE	0.028	0.050
Median	-0.031	-0.122
Min, Max	-0.43, 0.29	-0.43, 0.25

10-meter walk test speed (m/s) = 10 meters/mean time (seconds) taken to complete 2 assessments at each visit, imputed as 0 for patients unable to perform the walk; higher speeds indicate greater ambulatory function. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 4.5
10-meter Walk Test (10-MWT): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Previous Tetramer Stabilizer Use: Yes

Subgroup Visit	Vutrisiran (HELIOS-A) (N=75)	Patisiran (HELIOS-A) (N=33)
Baseline		
n	75	33
Mean (SD)	0.991 (0.394)	1.013 (0.433)
SE	0.045	0.075
Median	1.010	1.000
Min, Max	0.20, 1.82	0.11, 1.93
Month 9		
Actual Value		
n	73	32
Mean (SD)	0.988 (0.429)	1.005 (0.503)
SE	0.050	0.089
Median	1.013	1.056
Min, Max	0.14, 1.82	0.00, 2.31
Change from baseline		
n	73	32
Mean (SD)	-0.002 (0.159)	-0.029 (0.211)
SE	0.019	0.037
Median	0.000	-0.028
Min, Max	-0.65, 0.42	-0.50, 0.38

10-meter walk test speed (m/s) = 10 meters/mean time (seconds) taken to complete 2 assessments at each visit, imputed as 0 for patients unable to perform the walk; higher speeds indicate greater ambulatory function. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Alnylam Pharmaceuticals Inc.
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Table 4.5
10-meter Walk Test (10-MWT): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Previous Tetramer Stabilizer Use: Yes

Subgroup Visit	Vutrisiran (HELIOS-A) (N=75)	Patisiran (HELIOS-A) (N=33)
Month 18		
Actual Value		
n	71	31
Mean (SD)	0.989 (0.448)	1.001 (0.515)
SE	0.053	0.092
Median	1.053	1.111
Min, Max	0.00, 1.84	0.00, 2.19
Change from baseline		
n	71	31
Mean (SD)	-0.019 (0.259)	-0.054 (0.288)
SE	0.031	0.052
Median	0.006	-0.040
Min, Max	-0.77, 0.44	-0.95, 0.45

10-meter walk test speed (m/s) = 10 meters/mean time (seconds) taken to complete 2 assessments at each visit, imputed as 0 for patients unable to perform the walk; higher speeds indicate greater ambulatory function. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Alnylam Pharmaceuticals Inc.
ALN-TTRSC02-002

Table 4.5
10-meter Walk Test (10-MWT): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Previous Tetramer Stabilizer Use: No

Subgroup Visit	Vutrisiran (HELIOS-A) (N=47)	Patisiran (HELIOS-A) (N=9)
Baseline		
n	47	9
Mean (SD)	1.029 (0.394)	1.006 (0.261)
SE	0.058	0.087
Median	1.075	1.000
Min, Max	0.08, 1.87	0.61, 1.43
Month 9		
Actual Value		
n	42	8
Mean (SD)	1.081 (0.461)	0.961 (0.322)
SE	0.071	0.114
Median	1.111	0.989
Min, Max	0.09, 2.32	0.49, 1.43
Change from baseline		
n	42	8
Mean (SD)	0.008 (0.221)	-0.069 (0.134)
SE	0.034	0.047
Median	0.027	-0.051
Min, Max	-0.41, 0.54	-0.36, 0.10

10-meter walk test speed (m/s) = 10 meters/mean time (seconds) taken to complete 2 assessments at each visit, imputed as 0 for patients unable to perform the walk; higher speeds indicate greater ambulatory function. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Alnylam Pharmaceuticals Inc.
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Table 4.5
10-meter Walk Test (10-MWT): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Previous Tetramer Stabilizer Use: No

Subgroup Visit	Vutrisiran (HELIOS-A) (N=47)	Patisiran (HELIOS-A) (N=9)
Month 18		
Actual Value		
n	42	7
Mean (SD)	1.066 (0.465)	1.031 (0.449)
SE	0.072	0.170
Median	1.053	1.000
Min, Max	0.00, 2.34	0.45, 1.67
Change from baseline		
n	42	7
Mean (SD)	-0.019 (0.265)	0.004 (0.232)
SE	0.041	0.088
Median	0.000	-0.012
Min, Max	-0.91, 0.72	-0.31, 0.37

10-meter walk test speed (m/s) = 10 meters/mean time (seconds) taken to complete 2 assessments at each visit, imputed as 0 for patients unable to perform the walk; higher speeds indicate greater ambulatory function. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Alnylam Pharmaceuticals Inc.
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Table 4.5
10-meter Walk Test (10-MWT): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Genotype: V30M

Subgroup Visit	Vutrisiran (HELIOS-A) (N=54)	Patisiran (HELIOS-A) (N=20)
Baseline		
n	54	20
Mean (SD)	1.029 (0.355)	1.037 (0.335)
SE	0.048	0.075
Median	1.009	0.971
Min, Max	0.26, 1.73	0.46, 1.58
Month 9		
Actual Value		
n	51	20
Mean (SD)	1.032 (0.403)	1.000 (0.373)
SE	0.056	0.083
Median	1.029	0.974
Min, Max	0.14, 1.81	0.08, 1.72
Change from baseline		
n	51	20
Mean (SD)	0.001 (0.211)	-0.037 (0.194)
SE	0.029	0.043
Median	0.000	-0.029
Min, Max	-0.65, 0.54	-0.43, 0.31

10-meter walk test speed (m/s) = 10 meters/mean time (seconds) taken to complete 2 assessments at each visit, imputed as 0 for patients unable to perform the walk; higher speeds indicate greater ambulatory function. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Alnylam Pharmaceuticals Inc.
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Table 4.5
10-meter Walk Test (10-MWT): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Genotype: V30M

Subgroup Visit	Vutrisiran (HELIOS-A) (N=54)	Patisiran (HELIOS-A) (N=20)
Month 18		
Actual Value		
n	52	20
Mean (SD)	1.052 (0.423)	0.983 (0.376)
SE	0.059	0.084
Median	1.053	0.924
Min, Max	0.12, 2.34	0.26, 1.86
Change from baseline		
n	52	20
Mean (SD)	0.010 (0.261)	-0.054 (0.202)
SE	0.036	0.045
Median	0.045	-0.050
Min, Max	-0.77, 0.72	-0.43, 0.45

10-meter walk test speed (m/s) = 10 meters/mean time (seconds) taken to complete 2 assessments at each visit, imputed as 0 for patients unable to perform the walk; higher speeds indicate greater ambulatory function. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Alnylam Pharmaceuticals Inc.
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Table 4.5
10-meter Walk Test (10-MWT): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Genotype: non-V30M

Subgroup Visit	Vutrisiran (HELIOS-A) (N=68)	Patisiran (HELIOS-A) (N=22)
Baseline		
n	68	22
Mean (SD)	0.987 (0.422)	0.988 (0.458)
SE	0.051	0.098
Median	1.053	1.026
Min, Max	0.08, 1.87	0.11, 1.93
Month 9		
Actual Value		
n	64	20
Mean (SD)	1.014 (0.472)	0.993 (0.559)
SE	0.059	0.125
Median	1.090	1.068
Min, Max	0.09, 2.32	0.00, 2.31
Change from baseline		
n	64	20
Mean (SD)	0.003 (0.160)	-0.037 (0.206)
SE	0.020	0.046
Median	0.002	-0.039
Min, Max	-0.41, 0.45	-0.50, 0.38

10-meter walk test speed (m/s) = 10 meters/mean time (seconds) taken to complete 2 assessments at each visit, imputed as 0 for patients unable to perform the walk; higher speeds indicate greater ambulatory function. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Alnylam Pharmaceuticals Inc.
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Table 4.5
10-meter Walk Test (10-MWT): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Genotype: non-V30M

Subgroup Visit	Vutrisiran (HELIOS-A) (N=68)	Patisiran (HELIOS-A) (N=22)
Month 18		
Actual Value		
n	61	18
Mean (SD)	0.988 (0.480)	1.032 (0.616)
SE	0.062	0.145
Median	1.053	1.149
Min, Max	0.00, 1.67	0.00, 2.19
Change from baseline		
n	61	18
Mean (SD)	-0.043 (0.259)	-0.032 (0.346)
SE	0.033	0.082
Median	-0.005	-0.012
Min, Max	-0.91, 0.43	-0.95, 0.43

10-meter walk test speed (m/s) = 10 meters/mean time (seconds) taken to complete 2 assessments at each visit, imputed as 0 for patients unable to perform the walk; higher speeds indicate greater ambulatory function. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Alnylam Pharmaceuticals Inc.
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Table 4.5
10-meter Walk Test (10-MWT): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

FAP Stage: I

Subgroup Visit	Vutrisiran (HELIOS-A) (N=84)	Patisiran (HELIOS-A) (N=31)
Baseline		
n	84	31
Mean (SD)	1.176 (0.289)	1.134 (0.337)
SE	0.031	0.061
Median	1.146	1.093
Min, Max	0.58, 1.87	0.50, 1.93
Month 9		
Actual Value		
n	81	30
Mean (SD)	1.209 (0.332)	1.139 (0.407)
SE	0.037	0.074
Median	1.176	1.111
Min, Max	0.56, 2.32	0.00, 2.31
Change from baseline		
n	81	30
Mean (SD)	0.030 (0.192)	-0.006 (0.207)
SE	0.021	0.038
Median	0.035	0.000
Min, Max	-0.65, 0.54	-0.50, 0.38

10-meter walk test speed (m/s) = 10 meters/mean time (seconds) taken to complete 2 assessments at each visit, imputed as 0 for patients unable to perform the walk; higher speeds indicate greater ambulatory function. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Alnylam Pharmaceuticals Inc.
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Table 4.5
10-meter Walk Test (10-MWT): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

FAP Stage: I

Subgroup Visit	Vutrisiran (HELIOS-A) (N=84)	Patisiran (HELIOS-A) (N=31)
Month 18		
Actual Value		
n	81	30
Mean (SD)	1.199 (0.343)	1.115 (0.477)
SE	0.038	0.087
Median	1.176	1.143
Min, Max	0.42, 2.34	0.00, 2.19
Change from baseline		
n	81	30
Mean (SD)	0.011 (0.268)	-0.030 (0.308)
SE	0.030	0.056
Median	0.026	-0.006
Min, Max	-0.77, 0.72	-0.95, 0.45

10-meter walk test speed (m/s) = 10 meters/mean time (seconds) taken to complete 2 assessments at each visit, imputed as 0 for patients unable to perform the walk; higher speeds indicate greater ambulatory function. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 4.5
10-meter Walk Test (10-MWT): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

FAP Stage: II&III

Subgroup Visit	Vutrisiran (HELIOS-A) (N=38)	Patisiran (HELIOS-A) (N=11)
Baseline		
n	38	11
Mean (SD)	0.629 (0.326)	0.664 (0.368)
SE	0.053	0.111
Median	0.533	0.613
Min, Max	0.08, 1.31	0.11, 1.33
Month 9		
Actual Value		
n	34	10
Mean (SD)	0.576 (0.337)	0.568 (0.384)
SE	0.058	0.121
Median	0.510	0.548
Min, Max	0.09, 1.37	0.07, 1.25
Change from baseline		
n	34	10
Mean (SD)	-0.065 (0.141)	-0.132 (0.134)
SE	0.024	0.042
Median	-0.051	-0.083
Min, Max	-0.40, 0.20	-0.38, -0.01

10-meter walk test speed (m/s) = 10 meters/mean time (seconds) taken to complete 2 assessments at each visit, imputed as 0 for patients unable to perform the walk; higher speeds indicate greater ambulatory function. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 4.5
10-meter Walk Test (10-MWT): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

FAP Stage: II&III

Subgroup Visit	Vutrisiran (HELIOS-A) (N=38)	Patisiran (HELIOS-A) (N=11)
Month 18		
Actual Value		
n	32	8
Mean (SD)	0.560 (0.375)	0.599 (0.354)
SE	0.066	0.125
Median	0.558	0.616
Min, Max	0.00, 1.34	0.08, 1.18
Change from baseline		
n	32	8
Mean (SD)	-0.094 (0.226)	-0.092 (0.078)
SE	0.040	0.028
Median	-0.056	-0.098
Min, Max	-0.91, 0.24	-0.20, 0.02

10-meter walk test speed (m/s) = 10 meters/mean time (seconds) taken to complete 2 assessments at each visit, imputed as 0 for patients unable to perform the walk; higher speeds indicate greater ambulatory function. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 4.5
10-meter Walk Test (10-MWT): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Cardiac Subpopulation: Yes

Subgroup Visit	Vutrisiran (HELIOS-A) (N=40)	Patisiran (HELIOS-A) (N=14)
Baseline		
n	40	14
Mean (SD)	0.845 (0.402)	0.871 (0.484)
SE	0.063	0.129
Median	0.907	0.799
Min, Max	0.08, 1.67	0.11, 1.93
Month 9		
Actual Value		
n	38	14
Mean (SD)	0.820 (0.419)	0.869 (0.644)
SE	0.068	0.172
Median	0.875	0.779
Min, Max	0.09, 1.56	0.00, 2.31
Change from baseline		
n	38	14
Mean (SD)	-0.035 (0.151)	-0.002 (0.215)
SE	0.024	0.057
Median	-0.010	-0.028
Min, Max	-0.41, 0.27	-0.50, 0.38

10-meter walk test speed (m/s) = 10 meters/mean time (seconds) taken to complete 2 assessments at each visit, imputed as 0 for patients unable to perform the walk; higher speeds indicate greater ambulatory function. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 4.5
10-meter Walk Test (10-MWT): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Cardiac Subpopulation: Yes

Subgroup Visit	Vutrisiran (HELIOS-A) (N=40)	Patisiran (HELIOS-A) (N=14)
Month 18		
Actual Value		
n	36	13
Mean (SD)	0.851 (0.459)	0.875 (0.577)
SE	0.077	0.160
Median	0.879	0.884
Min, Max	0.00, 1.60	0.07, 2.19
Change from baseline		
n	36	13
Mean (SD)	-0.039 (0.245)	-0.031 (0.183)
SE	0.041	0.051
Median	-0.003	-0.029
Min, Max	-0.77, 0.39	-0.43, 0.26

10-meter walk test speed (m/s) = 10 meters/mean time (seconds) taken to complete 2 assessments at each visit, imputed as 0 for patients unable to perform the walk; higher speeds indicate greater ambulatory function. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Alnylam Pharmaceuticals Inc.
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Table 4.5
10-meter Walk Test (10-MWT): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Cardiac Subpopulation: No

Subgroup Visit	Vutrisiran (HELIOS-A) (N=82)	Patisiran (HELIOS-A) (N=28)
Baseline		
n	82	28
Mean (SD)	1.084 (0.366)	1.081 (0.339)
SE	0.040	0.064
Median	1.108	1.006
Min, Max	0.20, 1.87	0.31, 1.65
Month 9		
Actual Value		
n	77	26
Mean (SD)	1.122 (0.419)	1.065 (0.337)
SE	0.048	0.066
Median	1.111	1.037
Min, Max	0.14, 2.32	0.08, 1.72
Change from baseline		
n	77	26
Mean (SD)	0.020 (0.195)	-0.056 (0.189)
SE	0.022	0.037
Median	0.031	-0.042
Min, Max	-0.65, 0.54	-0.43, 0.31

10-meter walk test speed (m/s) = 10 meters/mean time (seconds) taken to complete 2 assessments at each visit, imputed as 0 for patients unable to perform the walk; higher speeds indicate greater ambulatory function. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 4.5
10-meter Walk Test (10-MWT): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Cardiac Subpopulation: No

Subgroup Visit	Vutrisiran (HELIOS-A) (N=82)	Patisiran (HELIOS-A) (N=28)
Month 18		
Actual Value		
n	77	25
Mean (SD)	1.096 (0.433)	1.075 (0.448)
SE	0.049	0.090
Median	1.136	1.111
Min, Max	0.00, 2.34	0.00, 1.87
Change from baseline		
n	77	25
Mean (SD)	-0.009 (0.268)	-0.049 (0.318)
SE	0.031	0.064
Median	0.006	-0.040
Min, Max	-0.91, 0.72	-0.95, 0.45

10-meter walk test speed (m/s) = 10 meters/mean time (seconds) taken to complete 2 assessments at each visit, imputed as 0 for patients unable to perform the walk; higher speeds indicate greater ambulatory function. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Alnylam Pharmaceuticals Inc.
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Table 4.5
10-meter Walk Test (10-MWT): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Weight (kg): <65

Subgroup Visit	Vutrisiran (HELIOS-A) (N=46)	Patisiran (HELIOS-A) (N=15)
Baseline		
n	46	15
Mean (SD)	0.875 (0.342)	0.992 (0.247)
SE	0.050	0.064
Median	0.972	0.991
Min, Max	0.08, 1.57	0.50, 1.54
Month 9		
Actual Value		
n	43	15
Mean (SD)	0.889 (0.377)	0.943 (0.349)
SE	0.058	0.090
Median	0.952	0.949
Min, Max	0.09, 1.54	0.00, 1.43
Change from baseline		
n	43	15
Mean (SD)	0.020 (0.156)	-0.049 (0.205)
SE	0.024	0.053
Median	0.031	-0.048
Min, Max	-0.30, 0.54	-0.50, 0.32

10-meter walk test speed (m/s) = 10 meters/mean time (seconds) taken to complete 2 assessments at each visit, imputed as 0 for patients unable to perform the walk; higher speeds indicate greater ambulatory function. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 4.5
10-meter Walk Test (10-MWT): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Weight (kg): <65

Subgroup Visit	Vutrisiran (HELIOS-A) (N=46)	Patisiran (HELIOS-A) (N=15)
Month 18		
Actual Value		
n	41	15
Mean (SD)	0.914 (0.401)	0.825 (0.394)
SE	0.063	0.102
Median	0.884	0.884
Min, Max	0.00, 1.60	0.00, 1.30
Change from baseline		
n	41	15
Mean (SD)	-0.005 (0.218)	-0.167 (0.273)
SE	0.034	0.071
Median	0.010	-0.103
Min, Max	-0.49, 0.38	-0.95, 0.11

10-meter walk test speed (m/s) = 10 meters/mean time (seconds) taken to complete 2 assessments at each visit, imputed as 0 for patients unable to perform the walk; higher speeds indicate greater ambulatory function. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 4.5
10-meter Walk Test (10-MWT): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Weight (kg): ≥65

Subgroup Visit	Vutrisiran (HELIOS-A) (N=76)	Patisiran (HELIOS-A) (N=27)
Baseline		
n	76	27
Mean (SD)	1.085 (0.403)	1.022 (0.468)
SE	0.046	0.090
Median	1.121	1.053
Min, Max	0.20, 1.87	0.11, 1.93
Month 9		
Actual Value		
n	72	25
Mean (SD)	1.101 (0.459)	1.029 (0.533)
SE	0.054	0.107
Median	1.111	1.111
Min, Max	0.19, 2.32	0.07, 2.31
Change from baseline		
n	72	25
Mean (SD)	-0.009 (0.198)	-0.030 (0.196)
SE	0.023	0.039
Median	-0.002	-0.036
Min, Max	-0.65, 0.45	-0.43, 0.38

10-meter walk test speed (m/s) = 10 meters/mean time (seconds) taken to complete 2 assessments at each visit, imputed as 0 for patients unable to perform the walk; higher speeds indicate greater ambulatory function. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 4.5
10-meter Walk Test (10-MWT): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Weight (kg): ≥65

Subgroup Visit	Vutrisiran (HELIOS-A) (N=76)	Patisiran (HELIOS-A) (N=27)
Month 18		
Actual Value		
n	72	23
Mean (SD)	1.077 (0.475)	1.125 (0.530)
SE	0.056	0.111
Median	1.080	1.162
Min, Max	0.00, 2.34	0.08, 2.19
Change from baseline		
n	72	23
Mean (SD)	-0.026 (0.282)	0.037 (0.252)
SE	0.033	0.053
Median	0.000	-0.025
Min, Max	-0.91, 0.72	-0.49, 0.45

10-meter walk test speed (m/s) = 10 meters/mean time (seconds) taken to complete 2 assessments at each visit, imputed as 0 for patients unable to perform the walk; higher speeds indicate greater ambulatory function. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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T10MWT (Binäre Analyse)

Alnylam Pharmaceuticals Inc.
ALN-TTRSC02-002

Table 4.4
10-meter Walk Test (10-MWT) Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A)
Binary Subgroup Analysis
mITT Population

Month 9

Analysis Visit Statistics	Vutrisiran (HELIOS-A) (N=122)	Patisiran (HELIOS-A) (N=42)
Age (years)		
<65		
Patients included in analysis, N1	76	31
>0 point increase from baseline, n(%)	38 (50.0)	9 (29.0)
≤0 point increase from baseline, n(%)	35 (46.1)	21 (67.7)
Missing, n(%)	3 (3.9)	1 (3.2)
>0 point increase from baseline, (95% CI)	50.0 (38.8, 61.2)	29.0 (13.1, 45.0)
Percentage difference (Vutrisiran − Patisiran), (95% CI)	20.968 (1.431, 40.504)	
Odds ratio (Vutrisiran/Patisiran), (95% CI) [1]	2.444 (0.997, 5.991)	
Relative risk (Vutrisiran/Patisiran), (95% CI) [1]	1.722 (0.950, 3.121)	
P-value [2]	0.0731	

10-meter walk test speed (m/s) = 10 meters/mean time (seconds) taken to complete 2 assessments at each visit, imputed as 0 for patients unable to perform the walk; higher speeds indicate greater ambulatory function.
N1 = Patients with missing postbaseline values due to COVID-19 or after initiation of local standard treatment for hATTR amyloidosis were included in analysis.
[1] Based on unstratified analysis.
In estimation of the odds ratio and relative risk, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the percentage difference or p-value.
[2] p-value based on the Wald test testing whether the relative risk equals to 1.
[3] p-value from a logistic regression using the penalized likelihood estimation (the FIRTH option) and with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Table 4.4
10-meter Walk Test (10-MWT) Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A)
Binary Subgroup Analysis
mITT Population

Month 9

Analysis Visit Statistics	Vutrisiran (HELIOS-A) (N=122)	Patisiran (HELIOS-A) (N=42)
≥65		
Patients included in analysis, N1	46	11
>0 point increase from baseline, n(%)	17 (37.0)	4 (36.4)
≤0 point increase from baseline, n(%)	25 (54.3)	6 (54.5)
Missing, n(%)	4 (8.7)	1 (9.1)
>0 point increase from baseline, (95% CI)	37.0 (23.0, 50.9)	36.4 (7.9, 64.8)
Percentage difference (Vutrisiran – Patisiran), (95% CI)	0.593 (-31.072, 32.258)	
Odds ratio (Vutrisiran/Patisiran), (95% CI) [1]	1.026 (0.262, 4.023)	
Relative risk (Vutrisiran/Patisiran), (95% CI) [1]	1.016 (0.427, 2.421)	
P-value [2]	0.9709	
p-value of Treatment*Age [3]	0.2923	

10-meter walk test speed (m/s) = 10 meters/mean time (seconds) taken to complete 2 assessments at each visit, imputed as 0 for patients unable to perform the walk; higher speeds indicate greater ambulatory function.
N1 = Patients with missing postbaseline values due to COVID-19 or after initiation of local standard treatment for hATTR amyloidosis were included in analysis.
[1] Based on unstratified analysis.
In estimation of the odds ratio and relative risk, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the percentage difference or p-value.
[2] p-value based on the Wald test testing whether the relative risk equals to 1.
[3] p-value from a logistic regression using the penalized likelihood estimation (the FIRTH option) and with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Table 4.4
10-meter Walk Test (10-MWT) Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A)
Binary Subgroup Analysis
mITT Population

Month 18

Analysis Visit Statistics	Vutrisiran (HELIOS-A) (N=122)	Patisiran (HELIOS-A) (N=42)
Age (years)		
<65		
Patients included in analysis, N1	76	31
>0 point increase from baseline, n(%)	39 (51.3)	11 (35.5)
≤0 point increase from baseline, n(%)	35 (46.1)	18 (58.1)
Missing, n(%)	2 (2.6)	2 (6.5)
>0 point increase from baseline, (95% CI)	51.3 (40.1, 62.6)	35.5 (18.6, 52.3)
Percentage difference (Vutrisiran – Patisiran), (95% CI)	15.832 (-4.416, 36.079)	
Odds ratio (Vutrisiran/Patisiran), (95% CI) [1]	1.916 (0.809, 4.539)	
Relative risk (Vutrisiran/Patisiran), (95% CI) [1]	1.446 (0.857, 2.439)	
P-value [2]	0.1666	

10-meter walk test speed (m/s) = 10 meters/mean time (seconds) taken to complete 2 assessments at each visit, imputed as 0 for patients unable to perform the walk; higher speeds indicate greater ambulatory function.
N1 = Patients with missing postbaseline values due to COVID-19 or after initiation of local standard treatment for hATTR amyloidosis were included in analysis.
[1] Based on unstratified analysis.
In estimation of the odds ratio and relative risk, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the percentage difference or p-value.
[2] p-value based on the Wald test testing whether the relative risk equals to 1.
[3] p-value from a logistic regression using the penalized likelihood estimation (the FIRTH option) and with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Table 4.4
10-meter Walk Test (10-MWT) Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A)
Binary Subgroup Analysis
mITT Population

Month 18

Analysis Visit Statistics	Vutrisiran (HELIOS-A) (N=122)	Patisiran (HELIOS-A) (N=42)
≥65		
Patients included in analysis, N1	46	11
>0 point increase from baseline, n(%)	19 (41.3)	4 (36.4)
≤0 point increase from baseline, n(%)	20 (43.5)	5 (45.5)
Missing, n(%)	7 (15.2)	2 (18.2)
>0 point increase from baseline, (95% CI)	41.3 (27.1, 55.5)	36.4 (7.9, 64.8)
Percentage difference (Vutrisiran – Patisiran), (95% CI)	4.941 (-26.849, 36.730)	
Odds ratio (Vutrisiran/Patisiran), (95% CI) [1]	1.231 (0.316, 4.805)	
Relative risk (Vutrisiran/Patisiran), (95% CI) [1]	1.136 (0.483, 2.669)	
P-value [2]	0.7701	
p-value of Treatment*Age [3]	0.5719	

10-meter walk test speed (m/s) = 10 meters/mean time (seconds) taken to complete 2 assessments at each visit, imputed as 0 for patients unable to perform the walk; higher speeds indicate greater ambulatory function.
N1 = Patients with missing postbaseline values due to COVID-19 or after initiation of local standard treatment for hATTR amyloidosis were included in analysis.
[1] Based on unstratified analysis.
In estimation of the odds ratio and relative risk, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the percentage difference or p-value.
[2] p-value based on the Wald test testing whether the relative risk equals to 1.
[3] p-value from a logistic regression using the penalized likelihood estimation (the FIRTH option) and with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Table 4.4
10-meter Walk Test (10-MWT) Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A)
Binary Subgroup Analysis
mITT Population

Month 9

Analysis Visit Statistics	Vutrisiran (HELIOS-A) (N=122)	Patisiran (HELIOS-A) (N=42)
Sex		
Male		
Patients included in analysis, N1	79	27
>0 point increase from baseline, n(%)	36 (45.6)	8 (29.6)
≤0 point increase from baseline, n(%)	40 (50.6)	17 (63.0)
Missing, n(%)	3 (3.8)	2 (7.4)
>0 point increase from baseline, (95% CI)	45.6 (34.6, 56.6)	29.6 (12.4, 46.9)
Percentage difference (Vutrisiran – Patisiran), (95% CI)	15.940 (-4.487, 36.367)	
Odds ratio (Vutrisiran/Patisiran), (95% CI) [1]	1.988 (0.779, 5.076)	
Relative risk (Vutrisiran/Patisiran), (95% CI) [1]	1.538 (0.820, 2.886)	
P-value [2]	0.1800	

10-meter walk test speed (m/s) = 10 meters/mean time (seconds) taken to complete 2 assessments at each visit, imputed as 0 for patients unable to perform the walk; higher speeds indicate greater ambulatory function.
N1 = Patients with missing postbaseline values due to COVID-19 or after initiation of local standard treatment for hATTR amyloidosis were included in analysis.
[1] Based on unstratified analysis.
In estimation of the odds ratio and relative risk, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the percentage difference or p-value.
[2] p-value based on the Wald test testing whether the relative risk equals to 1.
[3] p-value from a logistic regression using the penalized likelihood estimation (the FIRTH option) and with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Table 4.4
10-meter Walk Test (10-MWT) Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A)
Binary Subgroup Analysis
mITT Population

Month 9

Analysis Visit Statistics	Vutrisiran (HELIOS-A) (N=122)	Patisiran (HELIOS-A) (N=42)
Female		
Patients included in analysis, N1	43	15
>0 point increase from baseline, n(%)	19 (44.2)	5 (33.3)
≤0 point increase from baseline, n(%)	20 (46.5)	10 (66.7)
Missing, n(%)	4 (9.3)	0
>0 point increase from baseline, (95% CI)	44.2 (29.3, 59.0)	33.3 (9.5, 57.2)
Percentage difference (Vutrisiran – Patisiran), (95% CI)	10.853 (-17.244, 38.949)	
Odds ratio (Vutrisiran/Patisiran), (95% CI) [1]	1.583 (0.462, 5.421)	
Relative risk (Vutrisiran/Patisiran), (95% CI) [1]	1.326 (0.601, 2.923)	
P-value [2]	0.4847	
p-value of Treatment*Sex [3]	0.7632	

10-meter walk test speed (m/s) = 10 meters/mean time (seconds) taken to complete 2 assessments at each visit, imputed as 0 for patients unable to perform the walk; higher speeds indicate greater ambulatory function.
N1 = Patients with missing postbaseline values due to COVID-19 or after initiation of local standard treatment for hATTR amyloidosis were included in analysis.
[1] Based on unstratified analysis.
In estimation of the odds ratio and relative risk, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the percentage difference or p-value.
[2] p-value based on the Wald test testing whether the relative risk equals to 1.
[3] p-value from a logistic regression using the penalized likelihood estimation (the FIRTH option) and with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Table 4.4
10-meter Walk Test (10-MWT) Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A)
Binary Subgroup Analysis
mITT Population

Month 18

Analysis Visit Statistics	Vutrisiran (HELIOS-A) (N=122)	Patisiran (HELIOS-A) (N=42)
Sex		
Male		
Patients included in analysis, N1	79	27
>0 point increase from baseline, n(%)	36 (45.6)	9 (33.3)
≤0 point increase from baseline, n(%)	37 (46.8)	14 (51.9)
Missing, n(%)	6 (7.6)	4 (14.8)
>0 point increase from baseline, (95% CI)	45.6 (34.6, 56.6)	33.3 (15.6, 51.1)
Percentage difference (Vutrisiran – Patisiran), (95% CI)	12.236 (-8.663, 33.136)	
Odds ratio (Vutrisiran/Patisiran), (95% CI) [1]	1.674 (0.671, 4.179)	
Relative risk (Vutrisiran/Patisiran), (95% CI) [1]	1.367 (0.761, 2.455)	
P-value [2]	0.2951	

10-meter walk test speed (m/s) = 10 meters/mean time (seconds) taken to complete 2 assessments at each visit, imputed as 0 for patients unable to perform the walk; higher speeds indicate greater ambulatory function.
N1 = Patients with missing postbaseline values due to COVID-19 or after initiation of local standard treatment for hATTR amyloidosis were included in analysis.
[1] Based on unstratified analysis.
In estimation of the odds ratio and relative risk, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the percentage difference or p-value.
[2] p-value based on the Wald test testing whether the relative risk equals to 1.
[3] p-value from a logistic regression using the penalized likelihood estimation (the FIRTH option) and with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Table 4.4
10-meter Walk Test (10-MWT) Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A)
Binary Subgroup Analysis
mITT Population

Month 18

Analysis Visit Statistics	Vutrisiran (HELIOS-A) (N=122)	Patisiran (HELIOS-A) (N=42)
Female		
Patients included in analysis, N1	43	15
>0 point increase from baseline, n(%)	22 (51.2)	6 (40.0)
≤0 point increase from baseline, n(%)	18 (41.9)	9 (60.0)
Missing, n(%)	3 (7.0)	0
>0 point increase from baseline, (95% CI)	51.2 (36.2, 66.1)	40.0 (15.2, 64.8)
Percentage difference (Vutrisiran – Patisiran), (95% CI)	11.163 (-17.783, 40.108)	
Odds ratio (Vutrisiran/Patisiran), (95% CI) [1]	1.571 (0.476, 5.184)	
Relative risk (Vutrisiran/Patisiran), (95% CI) [1]	1.279 (0.645, 2.538)	
P-value [2]	0.4814	
p-value of Treatment*Sex [3]	0.9312	

10-meter walk test speed (m/s) = 10 meters/mean time (seconds) taken to complete 2 assessments at each visit, imputed as 0 for patients unable to perform the walk; higher speeds indicate greater ambulatory function.
N1 = Patients with missing postbaseline values due to COVID-19 or after initiation of local standard treatment for hATTR amyloidosis were included in analysis.
[1] Based on unstratified analysis.
In estimation of the odds ratio and relative risk, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the percentage difference or p-value.
[2] p-value based on the Wald test testing whether the relative risk equals to 1.
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Table 4.4
10-meter Walk Test (10-MWT) Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A)
Binary Subgroup Analysis
mITT Population

Month 9

Analysis Visit Statistics	Vutrisiran (HELIOS-A) (N=122)	Patisiran (HELIOS-A) (N=42)
Race		
White		
Patients included in analysis, N1	86	29
>0 point increase from baseline, n(%)	34 (39.5)	9 (31.0)
≤0 point increase from baseline, n(%)	47 (54.7)	19 (65.5)
Missing, n(%)	5 (5.8)	1 (3.4)
>0 point increase from baseline, (95% CI)	39.5 (29.2, 49.9)	31.0 (14.2, 47.9)
Percentage difference (Vutrisiran – Patisiran), (95% CI)	8.500 (-11.255, 28.256)	
Odds ratio (Vutrisiran/Patisiran), (95% CI) [1]	1.453 (0.592, 3.565)	
Relative risk (Vutrisiran/Patisiran), (95% CI) [1]	1.274 (0.698, 2.326)	
P-value [2]	0.4308	

10-meter walk test speed (m/s) = 10 meters/mean time (seconds) taken to complete 2 assessments at each visit, imputed as 0 for patients unable to perform the walk; higher speeds indicate greater ambulatory function.
N1 = Patients with missing postbaseline values due to COVID-19 or after initiation of local standard treatment for hATTR amyloidosis were included in analysis.
[1] Based on unstratified analysis.
In estimation of the odds ratio and relative risk, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the percentage difference or p-value.
[2] p-value based on the Wald test testing whether the relative risk equals to 1.
[3] p-value from a logistic regression using the penalized likelihood estimation (the FIRTH option) and with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Table 4.4
10-meter Walk Test (10-MWT) Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A)
Binary Subgroup Analysis
mITT Population

Month 9

Analysis Visit Statistics	Vutrisiran (HELIOS-A) (N=122)	Patisiran (HELIOS-A) (N=42)
All Other Races		
Patients included in analysis, N1	36	13
>0 point increase from baseline, n(%)	21 (58.3)	4 (30.8)
≤0 point increase from baseline, n(%)	13 (36.1)	8 (61.5)
Missing, n(%)	2 (5.6)	1 (7.7)
>0 point increase from baseline, (95% CI)	58.3 (42.2, 74.4)	30.8 (5.7, 55.9)
Percentage difference (Vutrisiran – Patisiran), (95% CI)	27.564 (-2.249, 57.377)	
Odds ratio (Vutrisiran/Patisiran), (95% CI) [1]	3.150 (0.815, 12.168)	
Relative risk (Vutrisiran/Patisiran), (95% CI) [1]	1.896 (0.802, 4.484)	
P-value [2]	0.1453	
p-value of Treatment*Race [3]	0.3773	

10-meter walk test speed (m/s) = 10 meters/mean time (seconds) taken to complete 2 assessments at each visit, imputed as 0 for patients unable to perform the walk; higher speeds indicate greater ambulatory function.
N1 = Patients with missing postbaseline values due to COVID-19 or after initiation of local standard treatment for hATTR amyloidosis were included in analysis.
[1] Based on unstratified analysis.
In estimation of the odds ratio and relative risk, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the percentage difference or p-value.
[2] p-value based on the Wald test testing whether the relative risk equals to 1.
[3] p-value from a logistic regression using the penalized likelihood estimation (the FIRTH option) and with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Table 4.4
10-meter Walk Test (10-MWT) Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A)
Binary Subgroup Analysis
mITT Population

Month 18

Analysis Visit Statistics	Vutrisiran (HELIOS-A) (N=122)	Patisiran (HELIOS-A) (N=42)
Race		
White		
Patients included in analysis, N1	86	29
>0 point increase from baseline, n(%)	38 (44.2)	11 (37.9)
≤0 point increase from baseline, n(%)	42 (48.8)	16 (55.2)
Missing, n(%)	6 (7.0)	2 (6.9)
>0 point increase from baseline, (95% CI)	44.2 (33.7, 54.7)	37.9 (20.3, 55.6)
Percentage difference (Vutrisiran – Patisiran), (95% CI)	6.255 (-14.288, 26.798)	
Odds ratio (Vutrisiran/Patisiran), (95% CI) [1]	1.295 (0.547, 3.069)	
Relative risk (Vutrisiran/Patisiran), (95% CI) [1]	1.165 (0.691, 1.965)	
P-value [2]	0.5671	

10-meter walk test speed (m/s) = 10 meters/mean time (seconds) taken to complete 2 assessments at each visit, imputed as 0 for patients unable to perform the walk; higher speeds indicate greater ambulatory function.
N1 = Patients with missing postbaseline values due to COVID-19 or after initiation of local standard treatment for hATTR amyloidosis were included in analysis.
[1] Based on unstratified analysis.
In estimation of the odds ratio and relative risk, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the percentage difference or p-value.
[2] p-value based on the Wald test testing whether the relative risk equals to 1.
[3] p-value from a logistic regression using the penalized likelihood estimation (the FIRTH option) and with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Table 4.4
10-meter Walk Test (10-MWT) Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A)
Binary Subgroup Analysis
mITT Population

Month 18

Analysis Visit Statistics	Vutrisiran (HELIOS-A) (N=122)	Patisiran (HELIOS-A) (N=42)
All Other Races		
Patients included in analysis, N1	36	13
>0 point increase from baseline, n(%)	20 (55.6)	4 (30.8)
≤0 point increase from baseline, n(%)	13 (36.1)	7 (53.8)
Missing, n(%)	3 (8.3)	2 (15.4)
>0 point increase from baseline, (95% CI)	55.6 (39.3, 71.8)	30.8 (5.7, 55.9)
Percentage difference (Vutrisiran – Patisiran), (95% CI)	24.786 (-5.096, 54.668)	
Odds ratio (Vutrisiran/Patisiran), (95% CI) [1]	2.813 (0.730, 10.836)	
Relative risk (Vutrisiran/Patisiran), (95% CI) [1]	1.806 (0.759, 4.293)	
P-value [2]	0.1812	
p-value of Treatment*Race [3]	0.3749	

10-meter walk test speed (m/s) = 10 meters/mean time (seconds) taken to complete 2 assessments at each visit, imputed as 0 for patients unable to perform the walk; higher speeds indicate greater ambulatory function.
N1 = Patients with missing postbaseline values due to COVID-19 or after initiation of local standard treatment for hATTR amyloidosis were included in analysis.
[1] Based on unstratified analysis.
In estimation of the odds ratio and relative risk, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the percentage difference or p-value.
[2] p-value based on the Wald test testing whether the relative risk equals to 1.
[3] p-value from a logistic regression using the penalized likelihood estimation (the FIRTH option) and with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Table 4.4
10-meter Walk Test (10-MWT) Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A)
Binary Subgroup Analysis
mITT Population

Month 9

Analysis Visit Statistics	Vutrisiran (HELIOS-A) (N=122)	Patisiran (HELIOS-A) (N=42)
Region		
North America		
Patients included in analysis, N1	27	8
>0 point increase from baseline, n(%)	11 (40.7)	2 (25.0)
≤0 point increase from baseline, n(%)	14 (51.9)	6 (75.0)
Missing, n(%)	2 (7.4)	0
>0 point increase from baseline, (95% CI)	40.7 (22.2, 59.3)	25.0 (0.0, 55.0)
Percentage difference (Vutrisiran – Patisiran), (95% CI)	15.741 (-19.527, 51.009)	
Odds ratio (Vutrisiran/Patisiran), (95% CI) [1]	2.063 (0.350, 12.168)	
Relative risk (Vutrisiran/Patisiran), (95% CI) [1]	1.630 (0.451, 5.882)	
P-value [2]	0.4558	

10-meter walk test speed (m/s) = 10 meters/mean time (seconds) taken to complete 2 assessments at each visit, imputed as 0 for patients unable to perform the walk; higher speeds indicate greater ambulatory function.
N1 = Patients with missing postbaseline values due to COVID-19 or after initiation of local standard treatment for hATTR amyloidosis were included in analysis.
[1] Based on unstratified analysis.
In estimation of the odds ratio and relative risk, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the percentage difference or p-value.
[2] p-value based on the Wald test testing whether the relative risk equals to 1.
[3] p-value from a logistic regression using the penalized likelihood estimation (the FIRTH option) and with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Binary Subgroup Analysis
mITT Population

Month 9

Analysis Visit Statistics	Vutrisiran (HELIOS-A) (N=122)	Patisiran (HELIOS-A) (N=42)
Western Europe		
Patients included in analysis, N1	42	20
>0 point increase from baseline, n(%)	12 (28.6)	7 (35.0)
≤0 point increase from baseline, n(%)	26 (61.9)	11 (55.0)
Missing, n(%)	4 (9.5)	2 (10.0)
>0 point increase from baseline, (95% CI)	28.6 (14.9, 42.2)	35.0 (14.1, 55.9)
Percentage difference (Vutrisiran – Patisiran), (95% CI)	-6.429 (-31.401, 18.544)	
Odds ratio (Vutrisiran/Patisiran), (95% CI) [1]	0.743 (0.238, 2.315)	
Relative risk (Vutrisiran/Patisiran), (95% CI) [1]	0.816 (0.380, 1.754)	
P-value [2]	0.6031	

10-meter walk test speed (m/s) = 10 meters/mean time (seconds) taken to complete 2 assessments at each visit, imputed as 0 for patients unable to perform the walk; higher speeds indicate greater ambulatory function.
N1 = Patients with missing postbaseline values due to COVID-19 or after initiation of local standard treatment for hATTR amyloidosis were included in analysis.
[1] Based on unstratified analysis.
In estimation of the odds ratio and relative risk, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the percentage difference or p-value.
[2] p-value based on the Wald test testing whether the relative risk equals to 1.
[3] p-value from a logistic regression using the penalized likelihood estimation (the FIRTH option) and with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Table 4.4
10-meter Walk Test (10-MWT) Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A)
Binary Subgroup Analysis
mITT Population

Month 9

Analysis Visit Statistics	Vutrisiran (HELIOS-A) (N=122)	Patisiran (HELIOS-A) (N=42)
Rest of World		
Patients included in analysis, N1	53	14
>0 point increase from baseline, n(%)	32 (60.4)	4 (28.6)
≤0 point increase from baseline, n(%)	20 (37.7)	10 (71.4)
Missing, n(%)	1 (1.9)	0
>0 point increase from baseline, (95% CI)	60.4 (47.2, 73.5)	28.6 (4.9, 52.2)
Percentage difference (Vutrisiran – Patisiran), (95% CI)	31.806 (4.725, 58.887)	
Odds ratio (Vutrisiran/Patisiran), (95% CI) [1]	3.810 (1.055, 13.750)	
Relative risk (Vutrisiran/Patisiran), (95% CI) [1]	2.113 (0.897, 4.976)	
P-value [2]	0.0869	
p-value of Treatment*Region [3]	0.1921	

10-meter walk test speed (m/s) = 10 meters/mean time (seconds) taken to complete 2 assessments at each visit, imputed as 0 for patients unable to perform the walk; higher speeds indicate greater ambulatory function.
N1 = Patients with missing postbaseline values due to COVID-19 or after initiation of local standard treatment for hATTR amyloidosis were included in analysis.
[1] Based on unstratified analysis.
In estimation of the odds ratio and relative risk, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the percentage difference or p-value.
[2] p-value based on the Wald test testing whether the relative risk equals to 1.
[3] p-value from a logistic regression using the penalized likelihood estimation (the FIRTH option) and with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Table 4.4
10-meter Walk Test (10-MWT) Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A)
Binary Subgroup Analysis
mITT Population

Month 18

Analysis Visit Statistics	Vutrisiran (HELIOS-A) (N=122)	Patisiran (HELIOS-A) (N=42)
Region		
North America		
Patients included in analysis, N1	27	8
>0 point increase from baseline, n(%)	15 (55.6)	4 (50.0)
≤0 point increase from baseline, n(%)	10 (37.0)	3 (37.5)
Missing, n(%)	2 (7.4)	1 (12.5)
>0 point increase from baseline, (95% CI)	55.6 (36.8, 74.3)	50.0 (15.4, 84.6)
Percentage difference (Vutrisiran – Patisiran), (95% CI)	5.556 (-33.837, 44.948)	
Odds ratio (Vutrisiran/Patisiran), (95% CI) [1]	1.250 (0.257, 6.070)	
Relative risk (Vutrisiran/Patisiran), (95% CI) [1]	1.111 (0.514, 2.401)	
P-value [2]	0.7887	

10-meter walk test speed (m/s) = 10 meters/mean time (seconds) taken to complete 2 assessments at each visit, imputed as 0 for patients unable to perform the walk; higher speeds indicate greater ambulatory function.
N1 = Patients with missing postbaseline values due to COVID-19 or after initiation of local standard treatment for hATTR amyloidosis were included in analysis.
[1] Based on unstratified analysis.
In estimation of the odds ratio and relative risk, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the percentage difference or p-value.
[2] p-value based on the Wald test testing whether the relative risk equals to 1.
[3] p-value from a logistic regression using the penalized likelihood estimation (the FIRTH option) and with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Table 4.4
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Binary Subgroup Analysis
mITT Population

Month 18

Analysis Visit Statistics	Vutrisiran (HELIOS-A) (N=122)	Patisiran (HELIOS-A) (N=42)
Western Europe		
Patients included in analysis, N1	42	20
>0 point increase from baseline, n(%)	13 (31.0)	7 (35.0)
≤0 point increase from baseline, n(%)	26 (61.9)	11 (55.0)
Missing, n(%)	3 (7.1)	2 (10.0)
>0 point increase from baseline, (95% CI)	31.0 (17.0, 44.9)	35.0 (14.1, 55.9)
Percentage difference (Vutrisiran – Patisiran), (95% CI)	-4.048 (-29.196, 21.101)	
Odds ratio (Vutrisiran/Patisiran), (95% CI) [1]	0.833 (0.269, 2.572)	
Relative risk (Vutrisiran/Patisiran), (95% CI) [1]	0.884 (0.418, 1.870)	
P-value [2]	0.7477	

10-meter walk test speed (m/s) = 10 meters/mean time (seconds) taken to complete 2 assessments at each visit, imputed as 0 for patients unable to perform the walk; higher speeds indicate greater ambulatory function.
N1 = Patients with missing postbaseline values due to COVID-19 or after initiation of local standard treatment for hATTR amyloidosis were included in analysis.
[1] Based on unstratified analysis.
In estimation of the odds ratio and relative risk, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the percentage difference or p-value.
[2] p-value based on the Wald test testing whether the relative risk equals to 1.
[3] p-value from a logistic regression using the penalized likelihood estimation (the FIRTH option) and with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Table 4.4
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Binary Subgroup Analysis
mITT Population

Month 18

Analysis Visit Statistics	Vutrisiran (HELIOS-A) (N=122)	Patisiran (HELIOS-A) (N=42)
Rest of World		
Patients included in analysis, N1	53	14
>0 point increase from baseline, n(%)	30 (56.6)	4 (28.6)
≤0 point increase from baseline, n(%)	19 (35.8)	9 (64.3)
Missing, n(%)	4 (7.5)	1 (7.1)
>0 point increase from baseline, (95% CI)	56.6 (43.3, 69.9)	28.6 (4.9, 52.2)
Percentage difference (Vutrisiran – Patisiran), (95% CI)	28.032 (0.866, 55.199)	
Odds ratio (Vutrisiran/Patisiran), (95% CI) [1]	3.261 (0.906, 11.734)	
Relative risk (Vutrisiran/Patisiran), (95% CI) [1]	1.981 (0.837, 4.687)	
P-value [2]	0.1197	
p-value of Treatment*Region [3]	0.3155	

10-meter walk test speed (m/s) = 10 meters/mean time (seconds) taken to complete 2 assessments at each visit, imputed as 0 for patients unable to perform the walk; higher speeds indicate greater ambulatory function.
N1 = Patients with missing postbaseline values due to COVID-19 or after initiation of local standard treatment for hATTR amyloidosis were included in analysis.
[1] Based on unstratified analysis.
In estimation of the odds ratio and relative risk, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the percentage difference or p-value.
[2] p-value based on the Wald test testing whether the relative risk equals to 1.
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Table 4.4
10-meter Walk Test (10-MWT) Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A)
Binary Subgroup Analysis
mITT Population

Month 9

Analysis Visit Statistics	Vutrisiran (HELIOS-A) (N=122)	Patisiran (HELIOS-A) (N=42)
Baseline NIS		
<50		
Patients included in analysis, N1	78	27
>0 point increase from baseline, n(%)	41 (52.6)	10 (37.0)
≤0 point increase from baseline, n(%)	35 (44.9)	17 (63.0)
Missing, n(%)	2 (2.6)	0
>0 point increase from baseline, (95% CI)	52.6 (41.5, 63.6)	37.0 (18.8, 55.3)
Percentage difference (Vutrisiran – Patisiran), (95% CI)	15.527 (-5.794, 36.848)	
Odds ratio (Vutrisiran/Patisiran), (95% CI) [1]	1.884 (0.767, 4.627)	
Relative risk (Vutrisiran/Patisiran), (95% CI) [1]	1.419 (0.831, 2.423)	
P-value [2]	0.1997	

10-meter walk test speed (m/s) = 10 meters/mean time (seconds) taken to complete 2 assessments at each visit, imputed as 0 for patients unable to perform the walk; higher speeds indicate greater ambulatory function.
N1 = Patients with missing postbaseline values due to COVID-19 or after initiation of local standard treatment for hATTR amyloidosis were included in analysis.
[1] Based on unstratified analysis.
In estimation of the odds ratio and relative risk, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the percentage difference or p-value.
[2] p-value based on the Wald test testing whether the relative risk equals to 1.
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Table 4.4
10-meter Walk Test (10-MWT) Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A)
Binary Subgroup Analysis
mITT Population

Month 9

Analysis Visit Statistics	Vutrisiran (HELIOS-A) (N=122)	Patisiran (HELIOS-A) (N=42)
≥50		
Patients included in analysis, N1	44	15
>0 point increase from baseline, n(%)	14 (31.8)	3 (20.0)
≤0 point increase from baseline, n(%)	25 (56.8)	10 (66.7)
Missing, n(%)	5 (11.4)	2 (13.3)
>0 point increase from baseline, (95% CI)	31.8 (18.1, 45.6)	20.0 (0.0, 40.2)
Percentage difference (Vutrisiran – Patisiran), (95% CI)	11.818 (-12.660, 36.296)	
Odds ratio (Vutrisiran/Patisiran), (95% CI) [1]	1.867 (0.453, 7.686)	
Relative risk (Vutrisiran/Patisiran), (95% CI) [1]	1.591 (0.529, 4.783)	
P-value [2]	0.4084	
p-value of Treatment*Baseline NIS [3]	0.9212	

10-meter walk test speed (m/s) = 10 meters/mean time (seconds) taken to complete 2 assessments at each visit, imputed as 0 for patients unable to perform the walk; higher speeds indicate greater ambulatory function.
N1 = Patients with missing postbaseline values due to COVID-19 or after initiation of local standard treatment for hATTR amyloidosis were included in analysis.
[1] Based on unstratified analysis.
In estimation of the odds ratio and relative risk, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the percentage difference or p-value.
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Table 4.4
10-meter Walk Test (10-MWT) Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A)
Binary Subgroup Analysis
mITT Population

Month 18

Analysis Visit Statistics	Vutrisiran (HELIOS-A) (N=122)	Patisiran (HELIOS-A) (N=42)
Baseline NIS		
<50		
Patients included in analysis, N1	78	27
>0 point increase from baseline, n(%)	42 (53.8)	12 (44.4)
≤0 point increase from baseline, n(%)	33 (42.3)	14 (51.9)
Missing, n(%)	3 (3.8)	1 (3.7)
>0 point increase from baseline, (95% CI)	53.8 (42.8, 64.9)	44.4 (25.7, 63.2)
Percentage difference (Vutrisiran – Patisiran), (95% CI)	9.402 (-12.363, 31.166)	
Odds ratio (Vutrisiran/Patisiran), (95% CI) [1]	1.458 (0.605, 3.516)	
Relative risk (Vutrisiran/Patisiran), (95% CI) [1]	1.212 (0.758, 1.937)	
P-value [2]	0.4227	

10-meter walk test speed (m/s) = 10 meters/mean time (seconds) taken to complete 2 assessments at each visit, imputed as 0 for patients unable to perform the walk; higher speeds indicate greater ambulatory function.
N1 = Patients with missing postbaseline values due to COVID-19 or after initiation of local standard treatment for hATTR amyloidosis were included in analysis.
[1] Based on unstratified analysis.
In estimation of the odds ratio and relative risk, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the percentage difference or p-value.
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Table 4.4
10-meter Walk Test (10-MWT) Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A)
Binary Subgroup Analysis
mITT Population

Month 18

Analysis Visit Statistics	Vutrisiran (HELIOS-A) (N=122)	Patisiran (HELIOS-A) (N=42)
≥50		
Patients included in analysis, N1	44	15
>0 point increase from baseline, n(%)	16 (36.4)	3 (20.0)
≤0 point increase from baseline, n(%)	22 (50.0)	9 (60.0)
Missing, n(%)	6 (13.6)	3 (20.0)
>0 point increase from baseline, (95% CI)	36.4 (22.1, 50.6)	20.0 (0.0, 40.2)
Percentage difference (Vutrisiran – Patisiran), (95% CI)	16.364 (-8.371, 41.098)	
Odds ratio (Vutrisiran/Patisiran), (95% CI) [1]	2.286 (0.560, 9.328)	
Relative risk (Vutrisiran/Patisiran), (95% CI) [1]	1.818 (0.614, 5.381)	
P-value [2]	0.2802	
p-value of Treatment*Baseline NIS [3]	0.6656	

10-meter walk test speed (m/s) = 10 meters/mean time (seconds) taken to complete 2 assessments at each visit, imputed as 0 for patients unable to perform the walk; higher speeds indicate greater ambulatory function.
N1 = Patients with missing postbaseline values due to COVID-19 or after initiation of local standard treatment for hATTR amyloidosis were included in analysis.
[1] Based on unstratified analysis.
In estimation of the odds ratio and relative risk, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the percentage difference or p-value.
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Table 4.4
10-meter Walk Test (10-MWT) Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A)
Binary Subgroup Analysis
mITT Population

Month 9

Analysis Visit Statistics	Vutrisiran (HELIOS-A) (N=122)	Patisiran (HELIOS-A) (N=42)
Previous Tetramer Stabilizer Use		
Yes		
Patients included in analysis, N1	75	33
>0 point increase from baseline, n(%)	32 (42.7)	12 (36.4)
≤0 point increase from baseline, n(%)	41 (54.7)	20 (60.6)
Missing, n(%)	2 (2.7)	1 (3.0)
>0 point increase from baseline, (95% CI)	42.7 (31.5, 53.9)	36.4 (20.0, 52.8)
Percentage difference (Vutrisiran – Patisiran), (95% CI)	6.303 (-13.563, 26.169)	
Odds ratio (Vutrisiran/Patisiran), (95% CI) [1]	1.302 (0.560, 3.029)	
Relative risk (Vutrisiran/Patisiran), (95% CI) [1]	1.173 (0.696, 1.978)	
P-value [2]	0.5484	

10-meter walk test speed (m/s) = 10 meters/mean time (seconds) taken to complete 2 assessments at each visit, imputed as 0 for patients unable to perform the walk; higher speeds indicate greater ambulatory function.
N1 = Patients with missing postbaseline values due to COVID-19 or after initiation of local standard treatment for hATTR amyloidosis were included in analysis.
[1] Based on unstratified analysis.
In estimation of the odds ratio and relative risk, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the percentage difference or p-value.
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Table 4.4
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Binary Subgroup Analysis
mITT Population

Month 9

Analysis Visit Statistics	Vutrisiran (HELIOS-A) (N=122)	Patisiran (HELIOS-A) (N=42)
No		
Patients included in analysis, N1	47	9
>0 point increase from baseline, n(%)	23 (48.9)	1 (11.1)
≤0 point increase from baseline, n(%)	19 (40.4)	7 (77.8)
Missing, n(%)	5 (10.6)	1 (11.1)
>0 point increase from baseline, (95% CI)	48.9 (34.6, 63.2)	11.1 (0.0, 31.6)
Percentage difference (Vutrisiran – Patisiran), (95% CI)	37.825 (12.809, 62.841)	
Odds ratio (Vutrisiran/Patisiran), (95% CI) [1]	7.667 (0.888, 66.219)	
Relative risk (Vutrisiran/Patisiran), (95% CI) [1]	4.404 (0.678, 28.599)	
P-value [2]	0.1204	
p-value of Treatment*Previous Tetramer Stabilizer Use [3]	0.1771	

10-meter walk test speed (m/s) = 10 meters/mean time (seconds) taken to complete 2 assessments at each visit, imputed as 0 for patients unable to perform the walk; higher speeds indicate greater ambulatory function.
N1 = Patients with missing postbaseline values due to COVID-19 or after initiation of local standard treatment for hATTR amyloidosis were included in analysis.
[1] Based on unstratified analysis.
In estimation of the odds ratio and relative risk, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the percentage difference or p-value.
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Binary Subgroup Analysis
mITT Population

Month 18

Analysis Visit Statistics	Vutrisiran (HELIOS-A) (N=122)	Patisiran (HELIOS-A) (N=42)
Previous Tetramer Stabilizer Use		
Yes		
Patients included in analysis, N1	75	33
>0 point increase from baseline, n(%)	37 (49.3)	13 (39.4)
≤0 point increase from baseline, n(%)	34 (45.3)	18 (54.5)
Missing, n(%)	4 (5.3)	2 (6.1)
>0 point increase from baseline, (95% CI)	49.3 (38.0, 60.6)	39.4 (22.7, 56.1)
Percentage difference (Vutrisiran – Patisiran), (95% CI)	9.939 (-10.209, 30.088)	
Odds ratio (Vutrisiran/Patisiran), (95% CI) [1]	1.498 (0.652, 3.443)	
Relative risk (Vutrisiran/Patisiran), (95% CI) [1]	1.252 (0.774, 2.027)	
P-value [2]	0.3596	

10-meter walk test speed (m/s) = 10 meters/mean time (seconds) taken to complete 2 assessments at each visit, imputed as 0 for patients unable to perform the walk; higher speeds indicate greater ambulatory function.
N1 = Patients with missing postbaseline values due to COVID-19 or after initiation of local standard treatment for hATTR amyloidosis were included in analysis.
[1] Based on unstratified analysis.
In estimation of the odds ratio and relative risk, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the percentage difference or p-value.
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Binary Subgroup Analysis
mITT Population

Month 18

Analysis Visit Statistics	Vutrisiran (HELIOS-A) (N=122)	Patisiran (HELIOS-A) (N=42)
No		
Patients included in analysis, N1	47	9
>0 point increase from baseline, n(%)	21 (44.7)	2 (22.2)
≤0 point increase from baseline, n(%)	21 (44.7)	5 (55.6)
Missing, n(%)	5 (10.6)	2 (22.2)
>0 point increase from baseline, (95% CI)	44.7 (30.5, 58.9)	22.2 (0.0, 49.4)
Percentage difference (Vutrisiran – Patisiran), (95% CI)	22.459 (-8.197, 53.114)	
Odds ratio (Vutrisiran/Patisiran), (95% CI) [1]	2.827 (0.530, 15.068)	
Relative risk (Vutrisiran/Patisiran), (95% CI) [1]	2.011 (0.569, 7.109)	
P-value [2]	0.2784	
p-value of Treatment*Previous Tetramer Stabilizer Use [3]	0.5907	

10-meter walk test speed (m/s) = 10 meters/mean time (seconds) taken to complete 2 assessments at each visit, imputed as 0 for patients unable to perform the walk; higher speeds indicate greater ambulatory function.
N1 = Patients with missing postbaseline values due to COVID-19 or after initiation of local standard treatment for hATTR amyloidosis were included in analysis.
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In estimation of the odds ratio and relative risk, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the percentage difference or p-value.
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ALN-TTRSC02-002

Table 4.4
10-meter Walk Test (10-MWT) Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A)
Binary Subgroup Analysis
mITT Population

Month 9

Analysis Visit Statistics	Vutrisiran (HELIOS-A) (N=122)	Patisiran (HELIOS-A) (N=42)
Genotype		
V30M		
Patients included in analysis, N1	54	20
>0 point increase from baseline, n(%)	23 (42.6)	7 (35.0)
≤0 point increase from baseline, n(%)	28 (51.9)	13 (65.0)
Missing, n(%)	3 (5.6)	0
>0 point increase from baseline, (95% CI)	42.6 (29.4, 55.8)	35.0 (14.1, 55.9)
Percentage difference (Vutrisiran – Patisiran), (95% CI)	7.593 (-17.124, 32.309)	
Odds ratio (Vutrisiran/Patisiran), (95% CI) [1]	1.378 (0.475, 3.999)	
Relative risk (Vutrisiran/Patisiran), (95% CI) [1]	1.217 (0.621, 2.385)	
P-value [2]	0.5673	

10-meter walk test speed (m/s) = 10 meters/mean time (seconds) taken to complete 2 assessments at each visit, imputed as 0 for patients unable to perform the walk; higher speeds indicate greater ambulatory function.
N1 = Patients with missing postbaseline values due to COVID-19 or after initiation of local standard treatment for hATTR amyloidosis were included in analysis.
[1] Based on unstratified analysis.
In estimation of the odds ratio and relative risk, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the percentage difference or p-value.
[2] p-value based on the Wald test testing whether the relative risk equals to 1.
[3] p-value from a logistic regression using the penalized likelihood estimation (the FIRTH option) and with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Table 4.4
10-meter Walk Test (10-MWT) Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A)
Binary Subgroup Analysis
mITT Population

Month 9

Analysis Visit Statistics	Vutrisiran (HELIOS-A) (N=122)	Patisiran (HELIOS-A) (N=42)
non-V30M		
Patients included in analysis, N1	68	22
>0 point increase from baseline, n(%)	32 (47.1)	6 (27.3)
≤0 point increase from baseline, n(%)	32 (47.1)	14 (63.6)
Missing, n(%)	4 (5.9)	2 (9.1)
>0 point increase from baseline, (95% CI)	47.1 (35.2, 58.9)	27.3 (8.7, 45.9)
Percentage difference (Vutrisiran – Patisiran), (95% CI)	19.786 (-2.284, 41.856)	
Odds ratio (Vutrisiran/Patisiran), (95% CI) [1]	2.370 (0.828, 6.788)	
Relative risk (Vutrisiran/Patisiran), (95% CI) [1]	1.725 (0.834, 3.571)	
P-value [2]	0.1416	
p-value of Treatment*Genotype [3]	0.4930	

10-meter walk test speed (m/s) = 10 meters/mean time (seconds) taken to complete 2 assessments at each visit, imputed as 0 for patients unable to perform the walk; higher speeds indicate greater ambulatory function.
N1 = Patients with missing postbaseline values due to COVID-19 or after initiation of local standard treatment for hATTR amyloidosis were included in analysis.
[1] Based on unstratified analysis.
In estimation of the odds ratio and relative risk, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the percentage difference or p-value.
[2] p-value based on the Wald test testing whether the relative risk equals to 1.
[3] p-value from a logistic regression using the penalized likelihood estimation (the FIRTH option) and with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Table 4.4
10-meter Walk Test (10-MWT) Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A)
Binary Subgroup Analysis
mITT Population

Month 18

Analysis Visit Statistics	Vutrisiran (HELIOS-A) (N=122)	Patisiran (HELIOS-A) (N=42)
Genotype		
V30M		
Patients included in analysis, N1	54	20
>0 point increase from baseline, n(%)	29 (53.7)	7 (35.0)
≤0 point increase from baseline, n(%)	23 (42.6)	13 (65.0)
Missing, n(%)	2 (3.7)	0
>0 point increase from baseline, (95% CI)	53.7 (40.4, 67.0)	35.0 (14.1, 55.9)
Percentage difference (Vutrisiran – Patisiran), (95% CI)	18.704 (-6.072, 43.479)	
Odds ratio (Vutrisiran/Patisiran), (95% CI) [1]	2.154 (0.744, 6.238)	
Relative risk (Vutrisiran/Patisiran), (95% CI) [1]	1.534 (0.804, 2.929)	
P-value [2]	0.1943	

10-meter walk test speed (m/s) = 10 meters/mean time (seconds) taken to complete 2 assessments at each visit, imputed as 0 for patients unable to perform the walk; higher speeds indicate greater ambulatory function.
N1 = Patients with missing postbaseline values due to COVID-19 or after initiation of local standard treatment for hATTR amyloidosis were included in analysis.
[1] Based on unstratified analysis.
In estimation of the odds ratio and relative risk, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the percentage difference or p-value.
[2] p-value based on the Wald test testing whether the relative risk equals to 1.
[3] p-value from a logistic regression using the penalized likelihood estimation (the FIRTH option) and with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Table 4.4
10-meter Walk Test (10-MWT) Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A)
Binary Subgroup Analysis
mITT Population

Month 18

Analysis Visit Statistics	Vutrisiran (HELIOS-A) (N=122)	Patisiran (HELIOS-A) (N=42)
non-V30M		
Patients included in analysis, N1	68	22
>0 point increase from baseline, n(%)	29 (42.6)	8 (36.4)
≤0 point increase from baseline, n(%)	32 (47.1)	10 (45.5)
Missing, n(%)	7 (10.3)	4 (18.2)
>0 point increase from baseline, (95% CI)	42.6 (30.9, 54.4)	36.4 (16.3, 56.5)
Percentage difference (Vutrisiran – Patisiran), (95% CI)	6.283 (-17.003, 29.569)	
Odds ratio (Vutrisiran/Patisiran), (95% CI) [1]	1.301 (0.482, 3.512)	
Relative risk (Vutrisiran/Patisiran), (95% CI) [1]	1.173 (0.632, 2.175)	
P-value [2]	0.6130	
p-value of Treatment*Genotype [3]	0.5066	

10-meter walk test speed (m/s) = 10 meters/mean time (seconds) taken to complete 2 assessments at each visit, imputed as 0 for patients unable to perform the walk; higher speeds indicate greater ambulatory function.
N1 = Patients with missing postbaseline values due to COVID-19 or after initiation of local standard treatment for hATTR amyloidosis were included in analysis.
[1] Based on unstratified analysis.
In estimation of the odds ratio and relative risk, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the percentage difference or p-value.
[2] p-value based on the Wald test testing whether the relative risk equals to 1.
[3] p-value from a logistic regression using the penalized likelihood estimation (the FIRTH option) and with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Table 4.4
10-meter Walk Test (10-MWT) Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A)
Binary Subgroup Analysis
mITT Population

Month 9

Analysis Visit Statistics	Vutrisiran (HELIOS-A) (N=122)	Patisiran (HELIOS-A) (N=42)
FAP Stage		
I		
Patients included in analysis, N1	84	31
>0 point increase from baseline, n(%)	44 (52.4)	13 (41.9)
≤0 point increase from baseline, n(%)	37 (44.0)	17 (54.8)
Missing, n(%)	3 (3.6)	1 (3.2)
>0 point increase from baseline, (95% CI)	52.4 (41.7, 63.1)	41.9 (24.6, 59.3)
Percentage difference (Vutrisiran – Patisiran), (95% CI)	10.445 (-9.946, 30.837)	
Odds ratio (Vutrisiran/Patisiran), (95% CI) [1]	1.523 (0.663, 3.500)	
Relative risk (Vutrisiran/Patisiran), (95% CI) [1]	1.249 (0.787, 1.982)	
P-value [2]	0.3451	

10-meter walk test speed (m/s) = 10 meters/mean time (seconds) taken to complete 2 assessments at each visit, imputed as 0 for patients unable to perform the walk; higher speeds indicate greater ambulatory function.
N1 = Patients with missing postbaseline values due to COVID-19 or after initiation of local standard treatment for hATTR amyloidosis were included in analysis.
[1] Based on unstratified analysis.
In estimation of the odds ratio and relative risk, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the percentage difference or p-value.
[2] p-value based on the Wald test testing whether the relative risk equals to 1.
[3] p-value from a logistic regression using the penalized likelihood estimation (the FIRTH option) and with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Table 4.4
10-meter Walk Test (10-MWT) Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A)
Binary Subgroup Analysis
mITT Population

Month 9

Analysis Visit Statistics	Vutrisiran (HELIOS-A) (N=122)	Patisiran (HELIOS-A) (N=42)
II&III		
Patients included in analysis, N1	38	11
>0 point increase from baseline, n(%)	11 (28.9)	0
≤0 point increase from baseline, n(%)	23 (60.5)	10 (90.9)
Missing, n(%)	4 (10.5)	1 (9.1)
>0 point increase from baseline, (95% CI)	28.9 (14.5, 43.4)	0.0 (0.0, 0.0)
Percentage difference (Vutrisiran – Patisiran), (95% CI)	28.947 (14.528, 43.367)	
Odds ratio (Vutrisiran/Patisiran), (95% CI) [1]	9.618 (0.522, 177.245)	
Relative risk (Vutrisiran/Patisiran), (95% CI) [1]	7.077 (0.449, 111.425)	
P-value [2]	0.1641	
p-value of Treatment*FAP Stage [3]	0.2486	

10-meter walk test speed (m/s) = 10 meters/mean time (seconds) taken to complete 2 assessments at each visit, imputed as 0 for patients unable to perform the walk; higher speeds indicate greater ambulatory function.
N1 = Patients with missing postbaseline values due to COVID-19 or after initiation of local standard treatment for hATTR amyloidosis were included in analysis.
[1] Based on unstratified analysis.
In estimation of the odds ratio and relative risk, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the percentage difference or p-value.
[2] p-value based on the Wald test testing whether the relative risk equals to 1.
[3] p-value from a logistic regression using the penalized likelihood estimation (the FIRTH option) and with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Table 4.4
10-meter Walk Test (10-MWT) Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A)
Binary Subgroup Analysis
mITT Population

Month 18

Analysis Visit Statistics	Vutrisiran (HELIOS-A) (N=122)	Patisiran (HELIOS-A) (N=42)
FAP Stage		
I		
Patients included in analysis, N1	84	31
>0 point increase from baseline, n(%)	44 (52.4)	14 (45.2)
≤0 point increase from baseline, n(%)	37 (44.0)	16 (51.6)
Missing, n(%)	3 (3.6)	1 (3.2)
>0 point increase from baseline, (95% CI)	52.4 (41.7, 63.1)	45.2 (27.6, 62.7)
Percentage difference (Vutrisiran – Patisiran), (95% CI)	7.220 (-13.298, 27.737)	
Odds ratio (Vutrisiran/Patisiran), (95% CI) [1]	1.336 (0.584, 3.054)	
Relative risk (Vutrisiran/Patisiran), (95% CI) [1]	1.160 (0.748, 1.798)	
P-value [2]	0.5072	

10-meter walk test speed (m/s) = 10 meters/mean time (seconds) taken to complete 2 assessments at each visit, imputed as 0 for patients unable to perform the walk; higher speeds indicate greater ambulatory function.
N1 = Patients with missing postbaseline values due to COVID-19 or after initiation of local standard treatment for hATTR amyloidosis were included in analysis.
[1] Based on unstratified analysis.
In estimation of the odds ratio and relative risk, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the percentage difference or p-value.
[2] p-value based on the Wald test testing whether the relative risk equals to 1.
[3] p-value from a logistic regression using the penalized likelihood estimation (the FIRTH option) and with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Table 4.4
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Binary Subgroup Analysis
mITT Population

Month 18

Analysis Visit Statistics	Vutrisiran (HELIOS-A) (N=122)	Patisiran (HELIOS-A) (N=42)
II&III		
Patients included in analysis, N1	38	11
>0 point increase from baseline, n(%)	14 (36.8)	1 (9.1)
≤0 point increase from baseline, n(%)	18 (47.4)	7 (63.6)
Missing, n(%)	6 (15.8)	3 (27.3)
>0 point increase from baseline, (95% CI)	36.8 (21.5, 52.2)	9.1 (0.0, 26.1)
Percentage difference (Vutrisiran – Patisiran), (95% CI)	27.751 (4.864, 50.639)	
Odds ratio (Vutrisiran/Patisiran), (95% CI) [1]	5.833 (0.674, 50.517)	
Relative risk (Vutrisiran/Patisiran), (95% CI) [1]	4.053 (0.597, 27.493)	
P-value [2]	0.1520	
p-value of Treatment*FAP Stage [3]	0.2820	

10-meter walk test speed (m/s) = 10 meters/mean time (seconds) taken to complete 2 assessments at each visit, imputed as 0 for patients unable to perform the walk; higher speeds indicate greater ambulatory function.
N1 = Patients with missing postbaseline values due to COVID-19 or after initiation of local standard treatment for hATTR amyloidosis were included in analysis.
[1] Based on unstratified analysis.
In estimation of the odds ratio and relative risk, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the percentage difference or p-value.
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Table 4.4
10-meter Walk Test (10-MWT) Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A)
Binary Subgroup Analysis
mITT Population

Month 9

Analysis Visit Statistics	Vutrisiran (HELIOS-A) (N=122)	Patisiran (HELIOS-A) (N=42)
Cardiac Subpopulation		
Yes		
Patients included in analysis, N1	40	14
>0 point increase from baseline, n(%)	16 (40.0)	6 (42.9)
≤0 point increase from baseline, n(%)	22 (55.0)	8 (57.1)
Missing, n(%)	2 (5.0)	0
>0 point increase from baseline, (95% CI)	40.0 (24.8, 55.2)	42.9 (16.9, 68.8)
Percentage difference (Vutrisiran – Patisiran), (95% CI)	-2.857 (-32.898, 27.184)	
Odds ratio (Vutrisiran/Patisiran), (95% CI) [1]	0.889 (0.259, 3.051)	
Relative risk (Vutrisiran/Patisiran), (95% CI) [1]	0.933 (0.457, 1.906)	
P-value [2]	0.8498	

10-meter walk test speed (m/s) = 10 meters/mean time (seconds) taken to complete 2 assessments at each visit, imputed as 0 for patients unable to perform the walk; higher speeds indicate greater ambulatory function.
N1 = Patients with missing postbaseline values due to COVID-19 or after initiation of local standard treatment for hATTR amyloidosis were included in analysis.
[1] Based on unstratified analysis.
In estimation of the odds ratio and relative risk, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the percentage difference or p-value.
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Table 4.4
10-meter Walk Test (10-MWT) Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A)
Binary Subgroup Analysis
mITT Population

Month 9

Analysis Visit Statistics	Vutrisiran (HELIOS-A) (N=122)	Patisiran (HELIOS-A) (N=42)
No		
Patients included in analysis, N1	82	28
>0 point increase from baseline, n(%)	39 (47.6)	7 (25.0)
≤0 point increase from baseline, n(%)	38 (46.3)	19 (67.9)
Missing, n(%)	5 (6.1)	2 (7.1)
>0 point increase from baseline, (95% CI)	47.6 (36.8, 58.4)	25.0 (9.0, 41.0)
Percentage difference (Vutrisiran – Patisiran), (95% CI)	22.561 (3.220, 41.902)	
Odds ratio (Vutrisiran/Patisiran), (95% CI) [1]	2.721 (1.043, 7.099)	
Relative risk (Vutrisiran/Patisiran), (95% CI) [1]	1.902 (0.963, 3.757)	
P-value [2]	0.0640	
p-value of Treatment*Cardiac Subpopulation [3]	0.1721	

10-meter walk test speed (m/s) = 10 meters/mean time (seconds) taken to complete 2 assessments at each visit, imputed as 0 for patients unable to perform the walk; higher speeds indicate greater ambulatory function.
N1 = Patients with missing postbaseline values due to COVID-19 or after initiation of local standard treatment for hATTR amyloidosis were included in analysis.
[1] Based on unstratified analysis.
In estimation of the odds ratio and relative risk, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the percentage difference or p-value.
[2] p-value based on the Wald test testing whether the relative risk equals to 1.
[3] p-value from a logistic regression using the penalized likelihood estimation (the FIRTH option) and with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Table 4.4
10-meter Walk Test (10-MWT) Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A)
Binary Subgroup Analysis
mITT Population

Month 18

Analysis Visit Statistics	Vutrisiran (HELIOS-A) (N=122)	Patisiran (HELIOS-A) (N=42)
Cardiac Subpopulation		
Yes		
Patients included in analysis, N1	40	14
>0 point increase from baseline, n(%)	17 (42.5)	5 (35.7)
≤0 point increase from baseline, n(%)	19 (47.5)	8 (57.1)
Missing, n(%)	4 (10.0)	1 (7.1)
>0 point increase from baseline, (95% CI)	42.5 (27.2, 57.8)	35.7 (10.6, 60.8)
Percentage difference (Vutrisiran – Patisiran), (95% CI)	6.786 (-22.619, 36.191)	
Odds ratio (Vutrisiran/Patisiran), (95% CI) [1]	1.330 (0.377, 4.691)	
Relative risk (Vutrisiran/Patisiran), (95% CI) [1]	1.190 (0.540, 2.622)	
P-value [2]	0.6660	

10-meter walk test speed (m/s) = 10 meters/mean time (seconds) taken to complete 2 assessments at each visit, imputed as 0 for patients unable to perform the walk; higher speeds indicate greater ambulatory function.
N1 = Patients with missing postbaseline values due to COVID-19 or after initiation of local standard treatment for hATTR amyloidosis were included in analysis.
[1] Based on unstratified analysis.
In estimation of the odds ratio and relative risk, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the percentage difference or p-value.
[2] p-value based on the Wald test testing whether the relative risk equals to 1.
[3] p-value from a logistic regression using the penalized likelihood estimation (the FIRTH option) and with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Table 4.4
10-meter Walk Test (10-MWT) Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A)
Binary Subgroup Analysis
mITT Population

Month 18

Analysis Visit Statistics	Vutrisiran (HELIOS-A) (N=122)	Patisiran (HELIOS-A) (N=42)
No		
Patients included in analysis, N1	82	28
>0 point increase from baseline, n(%)	41 (50.0)	10 (35.7)
≤0 point increase from baseline, n(%)	36 (43.9)	15 (53.6)
Missing, n(%)	5 (6.1)	3 (10.7)
>0 point increase from baseline, (95% CI)	50.0 (39.2, 60.8)	35.7 (18.0, 53.5)
Percentage difference (Vutrisiran – Patisiran), (95% CI)	14.286 (-6.501, 35.073)	
Odds ratio (Vutrisiran/Patisiran), (95% CI) [1]	1.800 (0.742, 4.366)	
Relative risk (Vutrisiran/Patisiran), (95% CI) [1]	1.400 (0.814, 2.407)	
P-value [2]	0.2237	
p-value of Treatment*Cardiac Subpopulation [3]	0.6879	

10-meter walk test speed (m/s) = 10 meters/mean time (seconds) taken to complete 2 assessments at each visit, imputed as 0 for patients unable to perform the walk; higher speeds indicate greater ambulatory function.
N1 = Patients with missing postbaseline values due to COVID-19 or after initiation of local standard treatment for hATTR amyloidosis were included in analysis.
[1] Based on unstratified analysis.
In estimation of the odds ratio and relative risk, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the percentage difference or p-value.
[2] p-value based on the Wald test testing whether the relative risk equals to 1.
[3] p-value from a logistic regression using the penalized likelihood estimation (the FIRTH option) and with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Table 4.4
10-meter Walk Test (10-MWT) Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A)
Binary Subgroup Analysis
mITT Population

Month 9

Analysis Visit Statistics	Vutrisiran (HELIOS-A) (N=122)	Patisiran (HELIOS-A) (N=42)
Weight (kg)		
<65 kg		
Patients included in analysis, N1	46	15
>0 point increase from baseline, n(%)	24 (52.2)	4 (26.7)
≤0 point increase from baseline, n(%)	19 (41.3)	11 (73.3)
Missing, n(%)	3 (6.5)	0
>0 point increase from baseline, (95% CI)	52.2 (37.7, 66.6)	26.7 (4.3, 49.0)
Percentage difference (Vutrisiran – Patisiran), (95% CI)	25.507 (-1.123, 52.138)	
Odds ratio (Vutrisiran/Patisiran), (95% CI) [1]	3.000 (0.832, 10.815)	
Relative risk (Vutrisiran/Patisiran), (95% CI) [1]	1.957 (0.809, 4.734)	
P-value [2]	0.1366	

10-meter walk test speed (m/s) = 10 meters/mean time (seconds) taken to complete 2 assessments at each visit, imputed as 0 for patients unable to perform the walk; higher speeds indicate greater ambulatory function.
N1 = Patients with missing postbaseline values due to COVID-19 or after initiation of local standard treatment for hATTR amyloidosis were included in analysis.
[1] Based on unstratified analysis.
In estimation of the odds ratio and relative risk, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the percentage difference or p-value.
[2] p-value based on the Wald test testing whether the relative risk equals to 1.
[3] p-value from a logistic regression using the penalized likelihood estimation (the FIRTH option) and with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

Alnylam Pharmaceuticals Inc.
ALN-TTRSC02-002

Table 4.4
10-meter Walk Test (10-MWT) Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A)
Binary Subgroup Analysis
mITT Population

Month 9

Analysis Visit Statistics	Vutrisiran (HELIOS-A) (N=122)	Patisiran (HELIOS-A) (N=42)
≥65 kg		
Patients included in analysis, N1	76	27
>0 point increase from baseline, n(%)	31 (40.8)	9 (33.3)
≤0 point increase from baseline, n(%)	41 (53.9)	16 (59.3)
Missing, n(%)	4 (5.3)	2 (7.4)
>0 point increase from baseline, (95% CI)	40.8 (29.7, 51.8)	33.3 (15.6, 51.1)
Percentage difference (Vutrisiran – Patisiran), (95% CI)	7.456 (-13.478, 28.390)	
Odds ratio (Vutrisiran/Patisiran), (95% CI) [1]	1.378 (0.548, 3.463)	
Relative risk (Vutrisiran/Patisiran), (95% CI) [1]	1.224 (0.673, 2.226)	
P-value [2]	0.5084	
p-value of Treatment*Weight (kg) [3]	0.3637	

10-meter walk test speed (m/s) = 10 meters/mean time (seconds) taken to complete 2 assessments at each visit, imputed as 0 for patients unable to perform the walk; higher speeds indicate greater ambulatory function.
N1 = Patients with missing postbaseline values due to COVID-19 or after initiation of local standard treatment for hATTR amyloidosis were included in analysis.
[1] Based on unstratified analysis.
In estimation of the odds ratio and relative risk, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the percentage difference or p-value.
[2] p-value based on the Wald test testing whether the relative risk equals to 1.
[3] p-value from a logistic regression using the penalized likelihood estimation (the FIRTH option) and with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

Alnylam Pharmaceuticals Inc.
ALN-TTRSC02-002

Table 4.4
10-meter Walk Test (10-MWT) Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A)
Binary Subgroup Analysis
mITT Population

Month 18

Analysis Visit Statistics	Vutrisiran (HELIOS-A) (N=122)	Patisiran (HELIOS-A) (N=42)
Weight (kg)		
<65 kg		
Patients included in analysis, N1	46	15
>0 point increase from baseline, n(%)	22 (47.8)	4 (26.7)
≤0 point increase from baseline, n(%)	19 (41.3)	11 (73.3)
Missing, n(%)	5 (10.9)	0
>0 point increase from baseline, (95% CI)	47.8 (33.4, 62.3)	26.7 (4.3, 49.0)
Percentage difference (Vutrisiran – Patisiran), (95% CI)	21.159 (-5.471, 47.790)	
Odds ratio (Vutrisiran/Patisiran), (95% CI) [1]	2.521 (0.699, 9.087)	
Relative risk (Vutrisiran/Patisiran), (95% CI) [1]	1.793 (0.735, 4.375)	
P-value [2]	0.1992	

10-meter walk test speed (m/s) = 10 meters/mean time (seconds) taken to complete 2 assessments at each visit, imputed as 0 for patients unable to perform the walk; higher speeds indicate greater ambulatory function.
N1 = Patients with missing postbaseline values due to COVID-19 or after initiation of local standard treatment for hATTR amyloidosis were included in analysis.
[1] Based on unstratified analysis.
In estimation of the odds ratio and relative risk, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the percentage difference or p-value.
[2] p-value based on the Wald test testing whether the relative risk equals to 1.
[3] p-value from a logistic regression using the penalized likelihood estimation (the FIRTH option) and with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

Alnylam Pharmaceuticals Inc.
ALN-TTRSC02-002

Table 4.4
10-meter Walk Test (10-MWT) Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A)
Binary Subgroup Analysis
mITT Population

Month 18

Analysis Visit Statistics	Vutrisiran (HELIOS-A) (N=122)	Patisiran (HELIOS-A) (N=42)
≥65 kg		
Patients included in analysis, N1	76	27
>0 point increase from baseline, n(%)	36 (47.4)	11 (40.7)
≤0 point increase from baseline, n(%)	36 (47.4)	12 (44.4)
Missing, n(%)	4 (5.3)	4 (14.8)
>0 point increase from baseline, (95% CI)	47.4 (36.1, 58.6)	40.7 (22.2, 59.3)
Percentage difference (Vutrisiran – Patisiran), (95% CI)	6.628 (-15.040, 28.296)	
Odds ratio (Vutrisiran/Patisiran), (95% CI) [1]	1.309 (0.538, 3.188)	
Relative risk (Vutrisiran/Patisiran), (95% CI) [1]	1.163 (0.696, 1.942)	
P-value [2]	0.5647	
p-value of Treatment*Weight (kg) [3]	0.4501	

10-meter walk test speed (m/s) = 10 meters/mean time (seconds) taken to complete 2 assessments at each visit, imputed as 0 for patients unable to perform the walk; higher speeds indicate greater ambulatory function.
N1 = Patients with missing postbaseline values due to COVID-19 or after initiation of local standard treatment for hATTR amyloidosis were included in analysis.
[1] Based on unstratified analysis.
In estimation of the odds ratio and relative risk, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the percentage difference or p-value.
[2] p-value based on the Wald test testing whether the relative risk equals to 1.
[3] p-value from a logistic regression using the penalized likelihood estimation (the FIRTH option) and with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

Subgruppenanalysen zum Endpunkt „Veränderung des allgemeinen Gesundheitszustandes gemessen anhand der EQ-5D-VAS“

EQ-5D-VAS (Kontinuierliche Analyse)

Alnylam Pharmaceuticals Inc.
ALN-TTRSC02-002

Table 7.3
EuroQol-Visual Analog Scale (EQ-VAS) Score: Change from Baseline to Month 18, MMRM Model
Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A) Subgroup Analysis
mITT Population

Subgroup Visit	LS Mean (95% CI) Vutrisiran (HELIOS-A) (N=122)	 Patisiran (HELIOS-A) (N=42)	LS Mean Difference (Vutrisiran-Patisiran) (95% CI), p-value	Standardized Effect Size (95% CI)
Age (years)				
<65	74	29		
Month 9	2.87 (-0.48, 6.21)	-1.89 (-7.32, 3.54)	4.76 (-1.61, 11.13), 0.1422	0.32 (-0.11, 0.76)
Month 18	2.58 (-0.75, 5.92)	-2.10 (-7.51, 3.31)	4.69 (-1.66, 11.03), 0.1465	0.32 (-0.11, 0.76)
≥65	42	10		
Month 9	2.86 (-1.40, 7.13)	-1.34 (-9.95, 7.26)	4.21 (-5.39, 13.80), 0.3883	0.26 (-0.42, 0.95)
Month 18	2.58 (-1.71, 6.87)	-1.55 (-10.24, 7.14)	4.13 (-5.55, 13.82), 0.4007	0.26 (-0.46, 0.97)
p-value of Treatment*Age	0.9201			

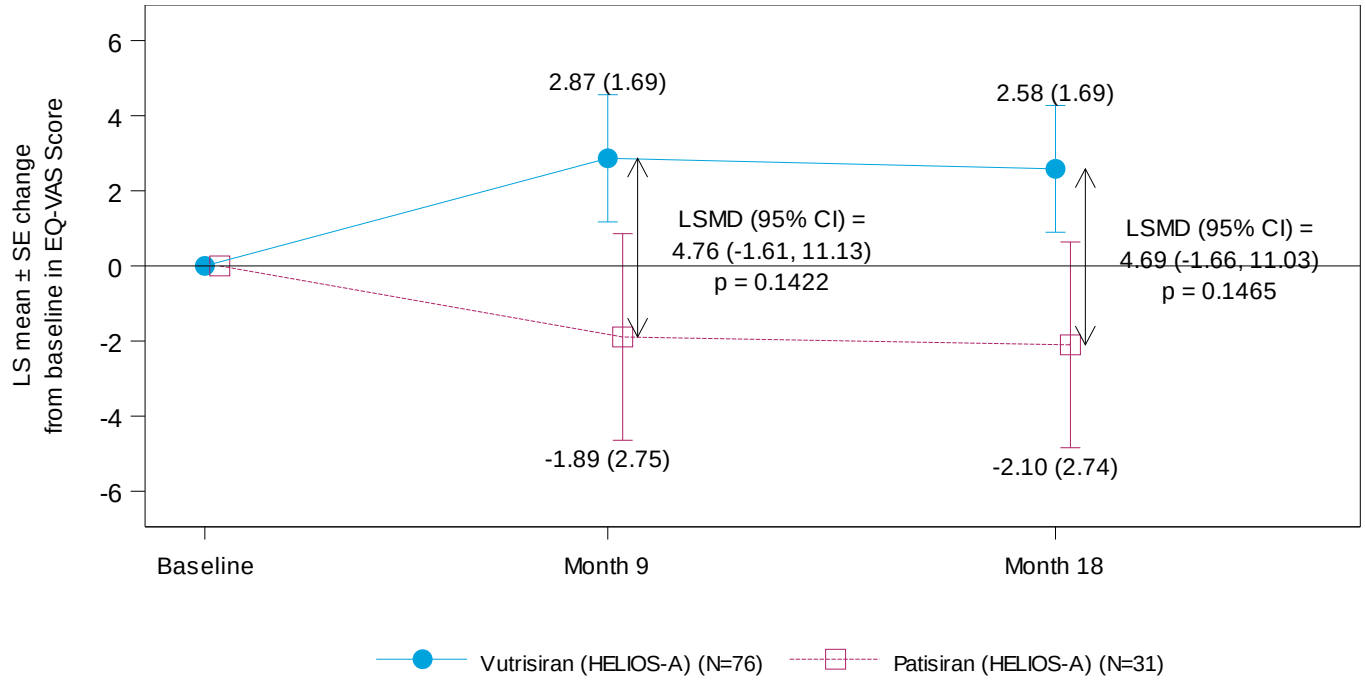
Higher scores indicate higher quality of life (range = 0 to 100). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.
LS estimates and p-value derived from mixed-effects model for repeated measures (MMRM), controlling for categorical factors (treatment, visit), the subgroup variable, continuous covariate (baseline value), and interaction (treatment by visit, treatment by subgroup).
Standardized effect size (d) = LS mean difference/estimated pooled standard deviation with the small sample bias correction.

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

Alnylam Pharmaceuticals Inc.
ALN-TTRSC02-002

EuroQol-Visual Analog Scale (EQ-VAS) Score Change from Baseline Over Time Series Plot
Subgroup Analysis: Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A)
mITT Population

Age (years): <65



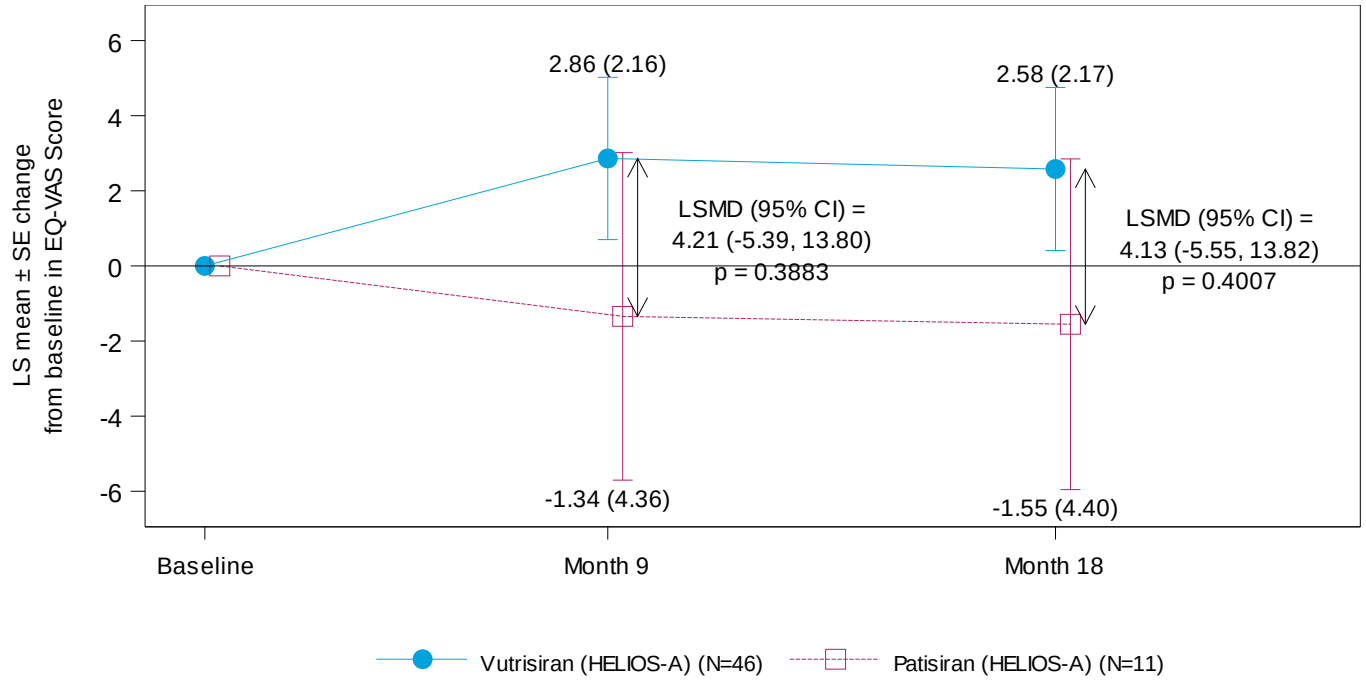
N evaluable			
Vutrisiran	75	73	73
Patisiran	30	28	28

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

Alnylam Pharmaceuticals Inc.
ALN-TTRSC02-002

EuroQol-Visual Analog Scale (EQ-VAS) Score Change from Baseline Over Time Series Plot
Subgroup Analysis: Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A)
mITT Population

Age (years): ≥65



N evaluable			
Vutrisiran	45	41	39
Patisiran	11	10	9

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

Alnylam Pharmaceuticals Inc.
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Table 7.3
EuroQol-Visual Analog Scale (EQ-VAS) Score: Change from Baseline to Month 18, MMRM Model
Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A) Subgroup Analysis
mITT Population

Subgroup Visit	LS Mean (95% CI) Vutrisiran (HELIOS-A) (N=122)	LS Mean (95% CI) Patisiran (HELIOS-A) (N=42)	LS Mean Difference (Vutrisiran-Patisiran) (95% CI), p-value	Standardized Effect Size (95% CI)
Sex				
Male	76	25		
Month 9	1.42 (-1.83, 4.68)	-1.21 (-6.86, 4.44)	2.64 (-3.89, 9.16), 0.4262	0.19 (-0.26, 0.64)
Month 18	1.13 (-2.16, 4.42)	-1.40 (-7.19, 4.39)	2.53 (-4.13, 9.19), 0.4538	0.17 (-0.29, 0.64)
Female	40	14		
Month 9	5.64 (1.32, 9.96)	-2.73 (-10.10, 4.64)	8.37 (-0.17, 16.90), 0.0546	0.49 (-0.14, 1.11)
Month 18	5.35 (1.01, 9.68)	-2.92 (-10.22, 4.39)	8.26 (-0.21, 16.74), 0.0560	0.52 (-0.08, 1.13)
p-value of Treatment*Sex	0.2607			

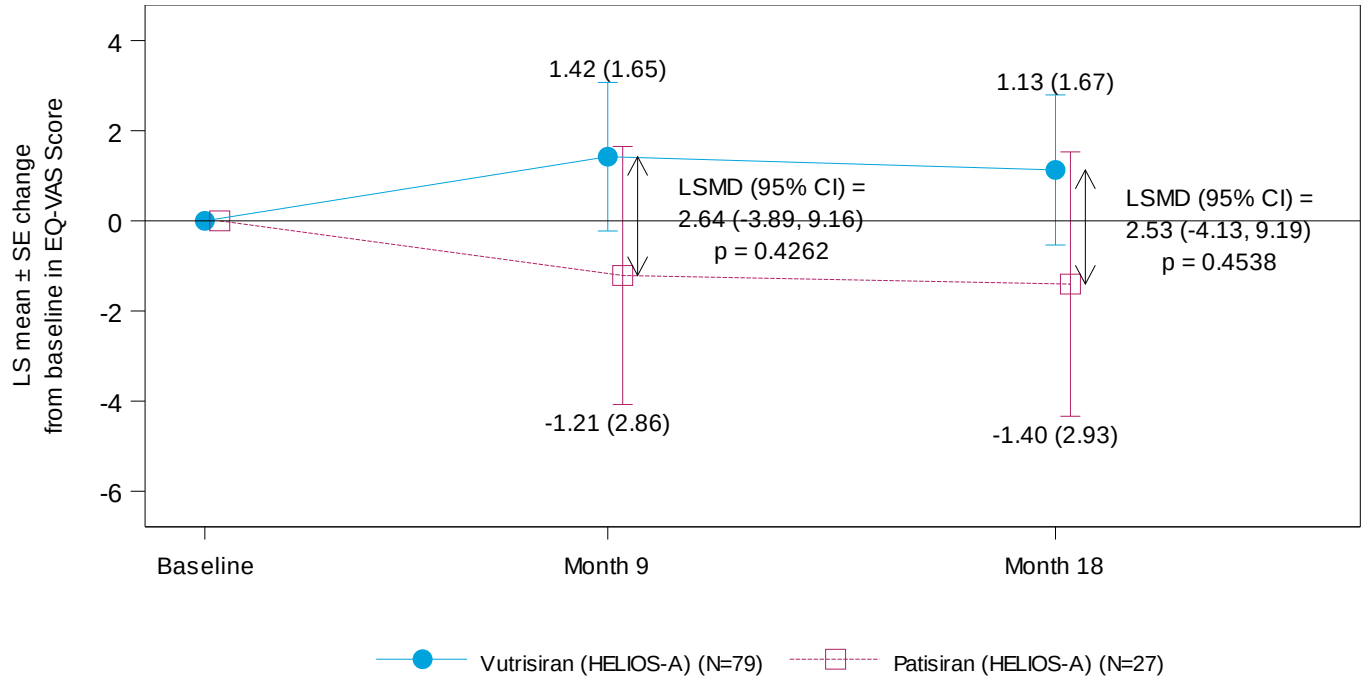
Higher scores indicate higher quality of life (range = 0 to 100). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.
LS estimates and p-value derived from mixed-effects model for repeated measures (MMRM), controlling for categorical factors (treatment, visit), the subgroup variable, continuous covariate (baseline value), and interaction (treatment by visit, treatment by subgroup).
Standardized effect size (d) = LS mean difference/estimated pooled standard deviation with the small sample bias correction.

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

Alnylam Pharmaceuticals Inc.
ALN-TTRSC02-002

EuroQol-Visual Analog Scale (EQ-VAS) Score Change from Baseline Over Time Series Plot
Subgroup Analysis: Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A)
mITT Population

Sex: Male



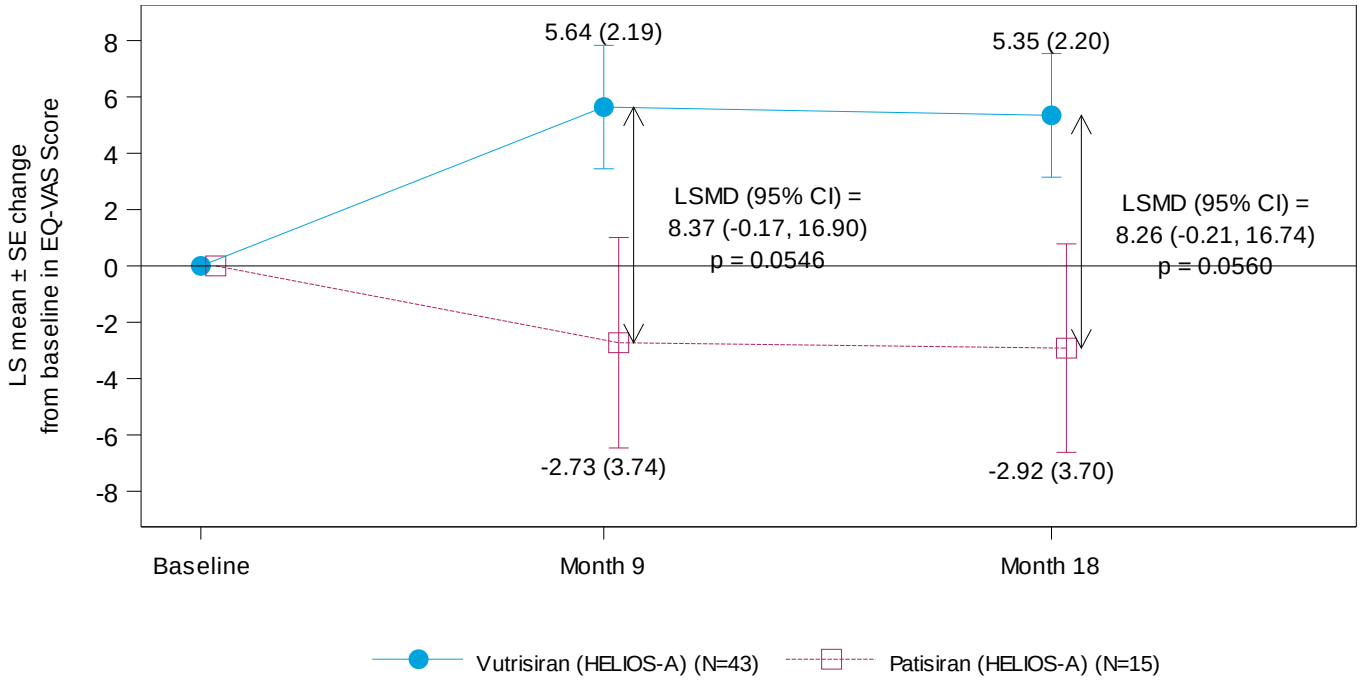
N evaluable			
Vutrisiran	78	75	73
Patisiran	27	25	23

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

Alnylam Pharmaceuticals Inc.
ALN-TTRSC02-002

EuroQol-Visual Analog Scale (EQ-VAS) Score Change from Baseline Over Time Series Plot
Subgroup Analysis: Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A)
mITT Population

Sex: Female



N evaluable			
Vutrisiran	42	39	39
Patisiran	14	13	14

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

Alnylam Pharmaceuticals Inc.
ALN-TTRSC02-002

Table 7.3
EuroQol-Visual Analog Scale (EQ-VAS) Score: Change from Baseline to Month 18, MMRM Model
Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A) Subgroup Analysis
mITT Population

Subgroup Visit	LS Mean (95% CI) Vutrisiran (HELIOS-A) (N=122)	LS Mean (95% CI) Patisiran (HELIOS-A) (N=42)	LS Mean Difference (Vutrisiran-Patisiran) (95% CI), p-value	Standardized Effect Size (95% CI)
Race				
White	81	27		
Month 9	1.66 (-1.51, 4.83)	-2.39 (-7.92, 3.14)	4.05 (-2.33, 10.42), 0.2117	0.29 (-0.15, 0.73)
Month 18	1.39 (-1.81, 4.58)	-2.59 (-8.14, 2.97)	3.97 (-2.44, 10.38), 0.2228	0.29 (-0.15, 0.74)
All Other Races	35	12		
Month 9	5.71 (1.10, 10.32)	-0.32 (-8.14, 7.51)	6.03 (-3.04, 15.09), 0.1910	0.36 (-0.29, 1.01)
Month 18	5.44 (0.80, 10.08)	-0.51 (-8.45, 7.42)	5.95 (-3.22, 15.13), 0.2019	0.32 (-0.35, 1.00)
p-value of Treatment*Race	0.7081			

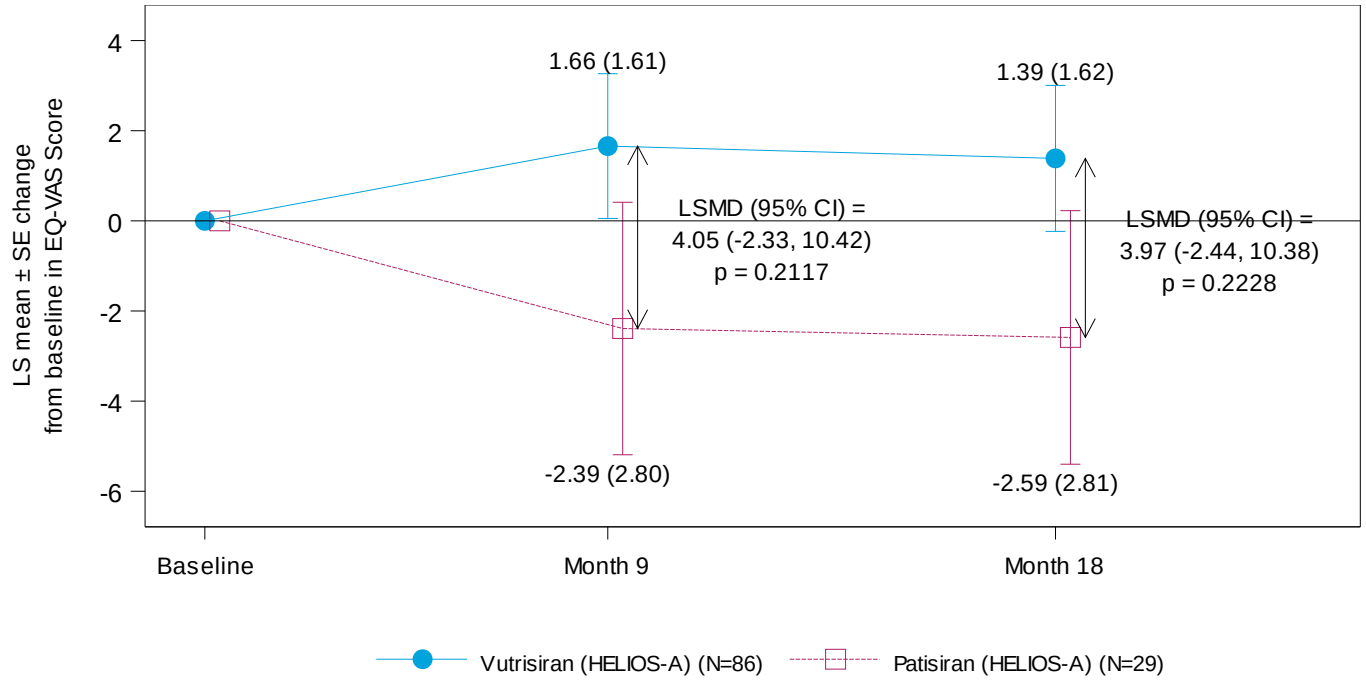
Higher scores indicate higher quality of life (range = 0 to 100). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.
LS estimates and p-value derived from mixed-effects model for repeated measures (MMRM), controlling for categorical factors (treatment, visit), the subgroup variable, continuous covariate (baseline value), and interaction (treatment by visit, treatment by subgroup).
Standardized effect size (d) = LS mean difference/estimated pooled standard deviation with the small sample bias correction.

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

Alnylam Pharmaceuticals Inc.
ALN-TTRSC02-002

EuroQol-Visual Analog Scale (EQ-VAS) Score Change from Baseline Over Time Series Plot
Subgroup Analysis: Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A)
mITT Population

Race: White



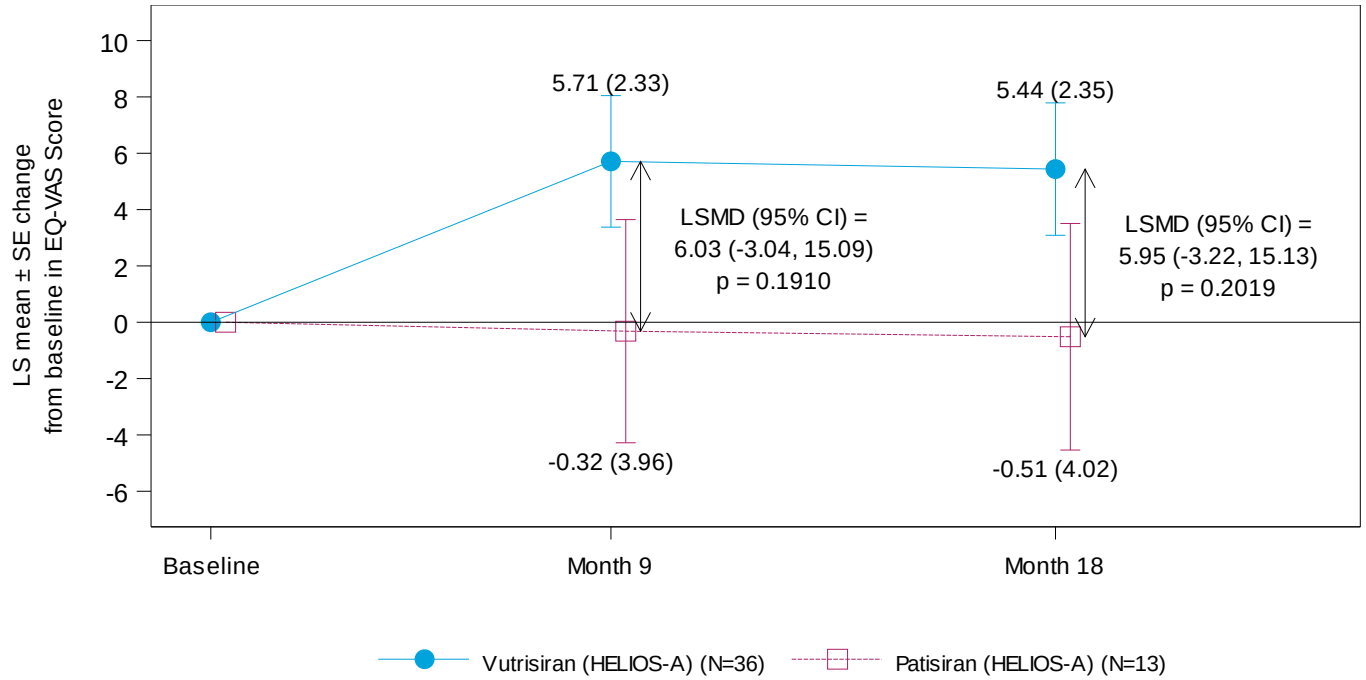
N evaluable			
Vutrisiran	84	80	79
Patisiran	28	26	26

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

Alnylam Pharmaceuticals Inc.
ALN-TTRSC02-002

EuroQol-Visual Analog Scale (EQ-VAS) Score Change from Baseline Over Time Series Plot
Subgroup Analysis: Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A)
mITT Population

Race: All Other Races



N evaluable			
Vutrisiran	36	34	33
Patisiran	13	12	11

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

Alnylam Pharmaceuticals Inc.
ALN-TTRSC02-002

Table 7.3
EuroQol-Visual Analog Scale (EQ-VAS) Score: Change from Baseline to Month 18, MMRM Model
Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A) Subgroup Analysis
mITT Population

Subgroup Visit	LS Mean (95% CI) Vutrisiran (HELIOS-A) (N=122)	LS Mean (95% CI) Patisiran (HELIOS-A) (N=42)	LS Mean Difference (Vutrisiran-Patisiran) (95% CI), p-value	Standardized Effect Size (95% CI)
Region				
North America	26	8		
Month 9	11.92 (6.77, 17.06)	0.87 (-8.27, 10.01)	11.05 (0.58, 21.52), 0.0387	1.05 (0.23, 1.87)
Month 18	11.62 (6.51, 16.72)	0.70 (-8.51, 9.90)	10.92 (0.42, 21.42), 0.0416	0.90 (0.05, 1.76)
Western Europe	38	17		
Month 9	-0.88 (-5.12, 3.36)	0.08 (-6.39, 6.55)	-0.96 (-8.69, 6.78), 0.8075	-0.07 (-0.63, 0.49)
Month 18	-1.18 (-5.37, 3.02)	-0.09 (-6.47, 6.29)	-1.08 (-8.72, 6.55), 0.7796	-0.08 (-0.64, 0.49)
Rest of World	52	14		
Month 9	1.32 (-2.38, 5.02)	-5.56 (-12.72, 1.59)	6.88 (-1.18, 14.95), 0.0938	0.40 (-0.21, 1.00)
Month 18	1.02 (-2.66, 4.70)	-5.73 (-12.81, 1.34)	6.75 (-1.23, 14.74), 0.0966	0.43 (-0.18, 1.04)
p-value of Treatment*Region	0.1212			

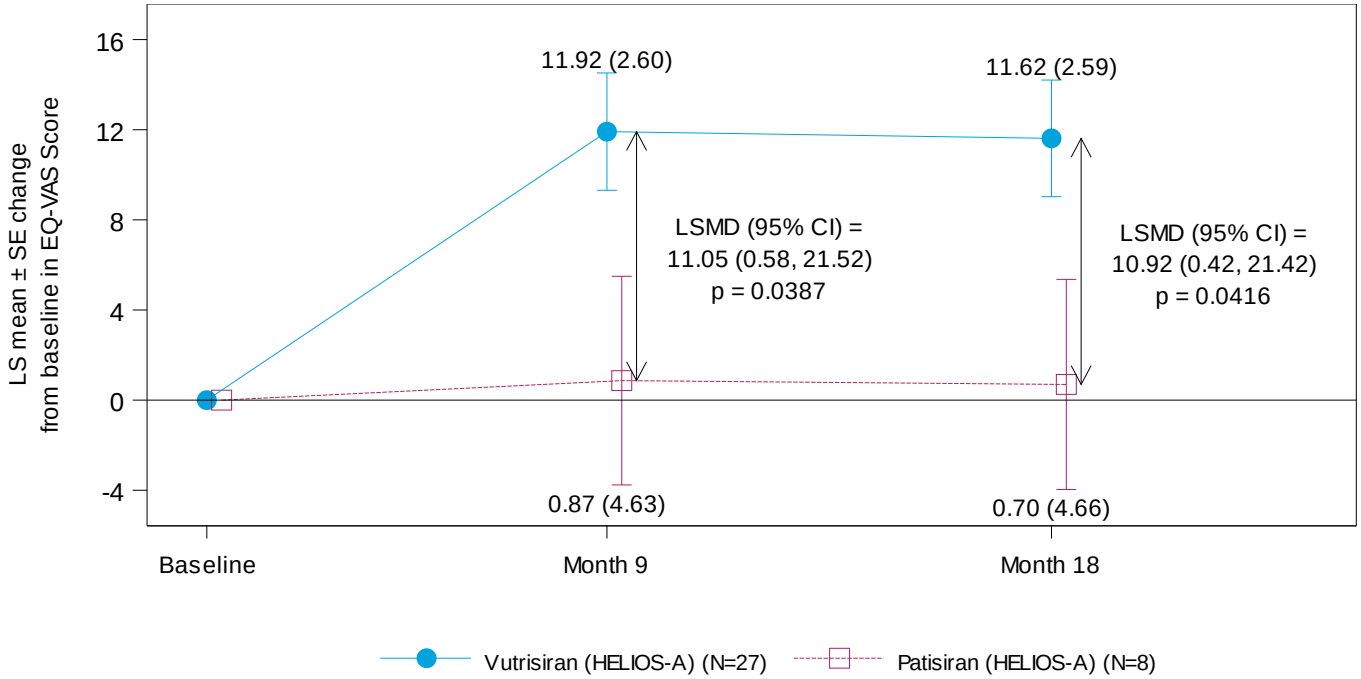
Higher scores indicate higher quality of life (range = 0 to 100). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.
LS estimates and p-value derived from mixed-effects model for repeated measures (MMRM), controlling for categorical factors (treatment, visit), the subgroup variable, continuous covariate (baseline value), and interaction (treatment by visit, treatment by subgroup).
Standardized effect size (d) = LS mean difference/estimated pooled standard deviation with the small sample bias correction.

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

Alnylam Pharmaceuticals Inc.
ALN-TTRSC02-002

EuroQol-Visual Analog Scale (EQ-VAS) Score Change from Baseline Over Time Series Plot
Subgroup Analysis: Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A)
mITT Population

Region: North America



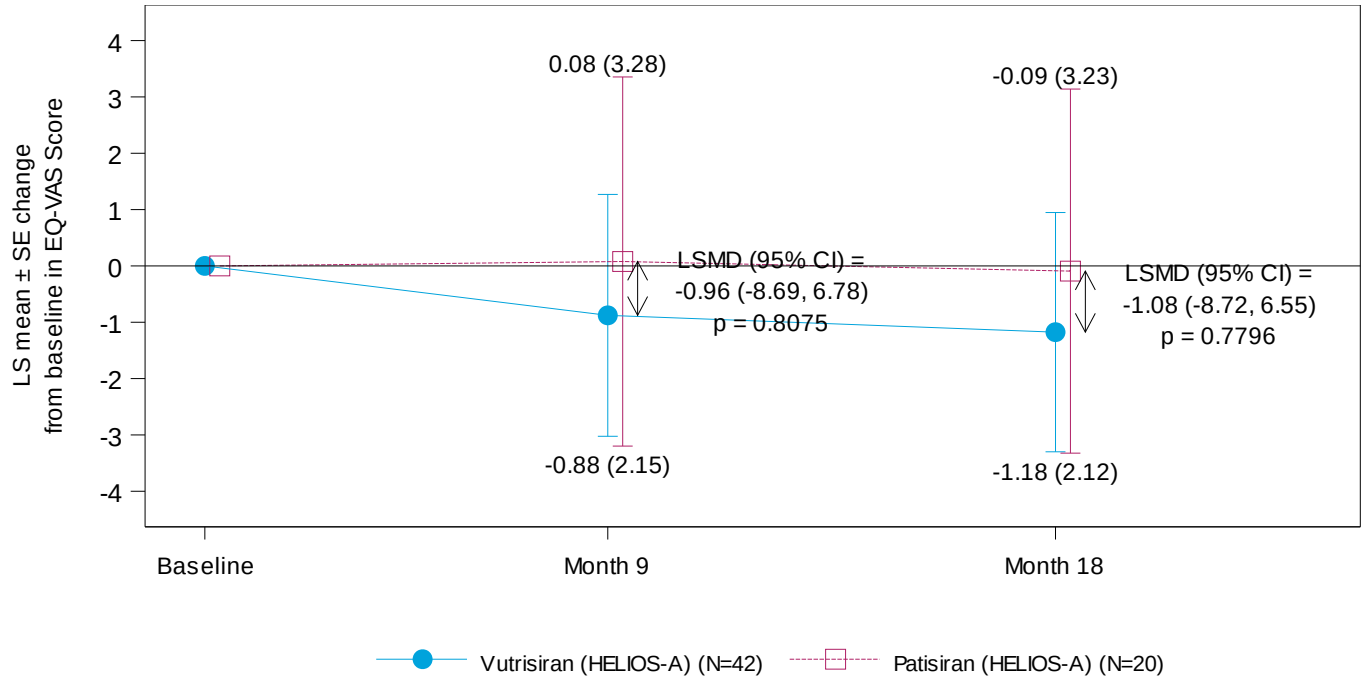
N evaluable			
Vutrisiran	26	24	24
Patisiran	8	8	7

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

Alnylam Pharmaceuticals Inc.
ALN-TTRSC02-002

EuroQol-Visual Analog Scale (EQ-VAS) Score Change from Baseline Over Time Series Plot
Subgroup Analysis: Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A)
mITT Population

Region: Western Europe



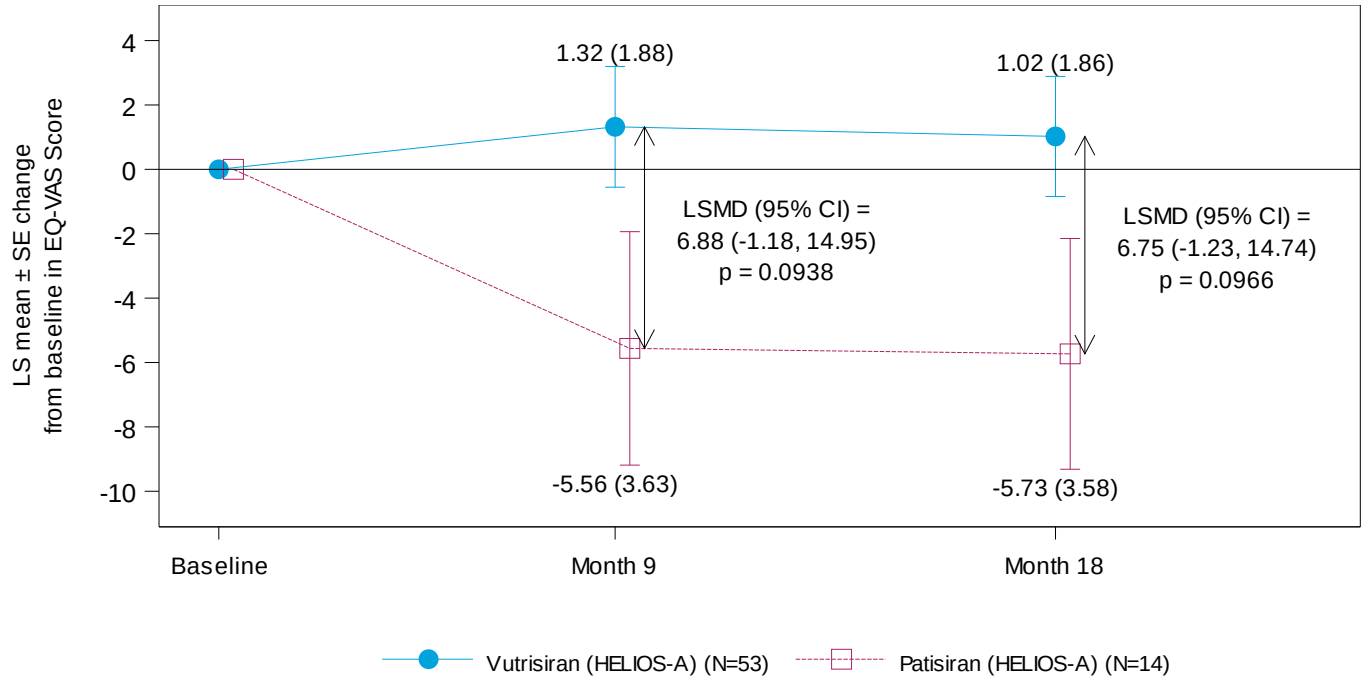
N evaluable			
Vutrisiran	41	38	38
Patisiran	19	17	17

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

Alnylam Pharmaceuticals Inc.
ALN-TTRSC02-002

EuroQol-Visual Analog Scale (EQ-VAS) Score Change from Baseline Over Time Series Plot
Subgroup Analysis: Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A)
mITT Population

Region: Rest of World



N evaluable			
Vutrisiran	53	52	50
Patisiran	14	13	13

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

Alnylam Pharmaceuticals Inc.
ALN-TTRSC02-002

Table 7.3
EuroQol-Visual Analog Scale (EQ-VAS) Score: Change from Baseline to Month 18, MMRM Model
Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A) Subgroup Analysis
mITT Population

Subgroup Visit	LS Mean (95% CI) Vutrisiran (HELIOS-A) (N=122)	LS Mean (95% CI) Patisiran (HELIOS-A) (N=42)	LS Mean Difference (Vutrisiran-Patisiran) (95% CI), p-value	Standardized Effect Size (95% CI)
Baseline NIS				
<50	76	26		
Month 9	8.42 (5.47, 11.37)	1.87 (-3.18, 6.93)	6.55 (0.75, 12.36), 0.0272	0.53 (0.08, 0.99)
Month 18	8.20 (5.23, 11.17)	1.60 (-3.46, 6.65)	6.60 (0.80, 12.40), 0.0259	0.49 (0.03, 0.95)
≥50	40	13		
Month 9	-7.56 (-11.45, -3.67)	-8.63 (-15.36, -1.90)	1.07 (-6.61, 8.74), 0.7842	0.07 (-0.55, 0.69)
Month 18	-7.79 (-11.67, -3.91)	-8.90 (-15.71, -2.10)	1.12 (-6.62, 8.86), 0.7760	0.08 (-0.56, 0.72)
p-value of Treatment*Baseline NIS	0.2217			

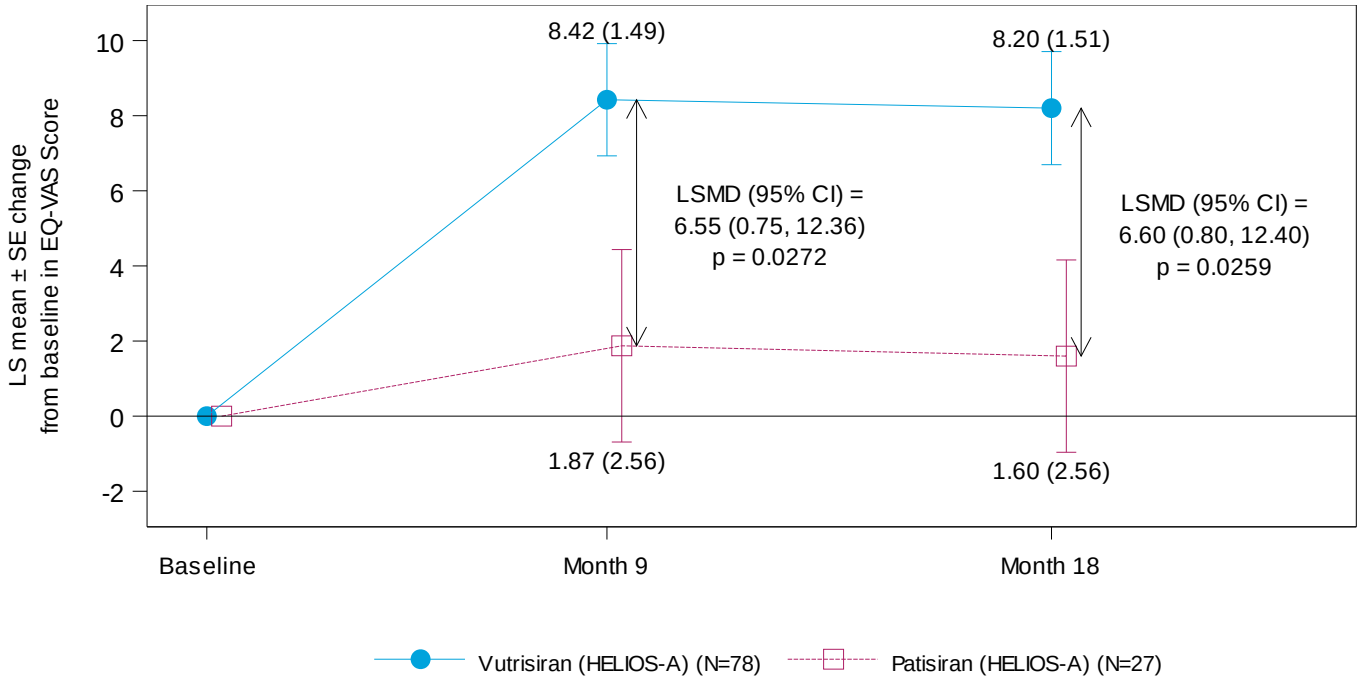
Higher scores indicate higher quality of life (range = 0 to 100). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.
LS estimates and p-value derived from mixed-effects model for repeated measures (MMRM), controlling for categorical factors (treatment, visit), the subgroup variable, continuous covariate (baseline value), and interaction (treatment by visit, treatment by subgroup).
Standardized effect size (d) = LS mean difference/estimated pooled standard deviation with the small sample bias correction.

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

Alnylam Pharmaceuticals Inc.
ALN-TTRSC02-002

EuroQol-Visual Analog Scale (EQ-VAS) Score Change from Baseline Over Time Series Plot
Subgroup Analysis: Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A)
mITT Population

Baseline NIS: <50



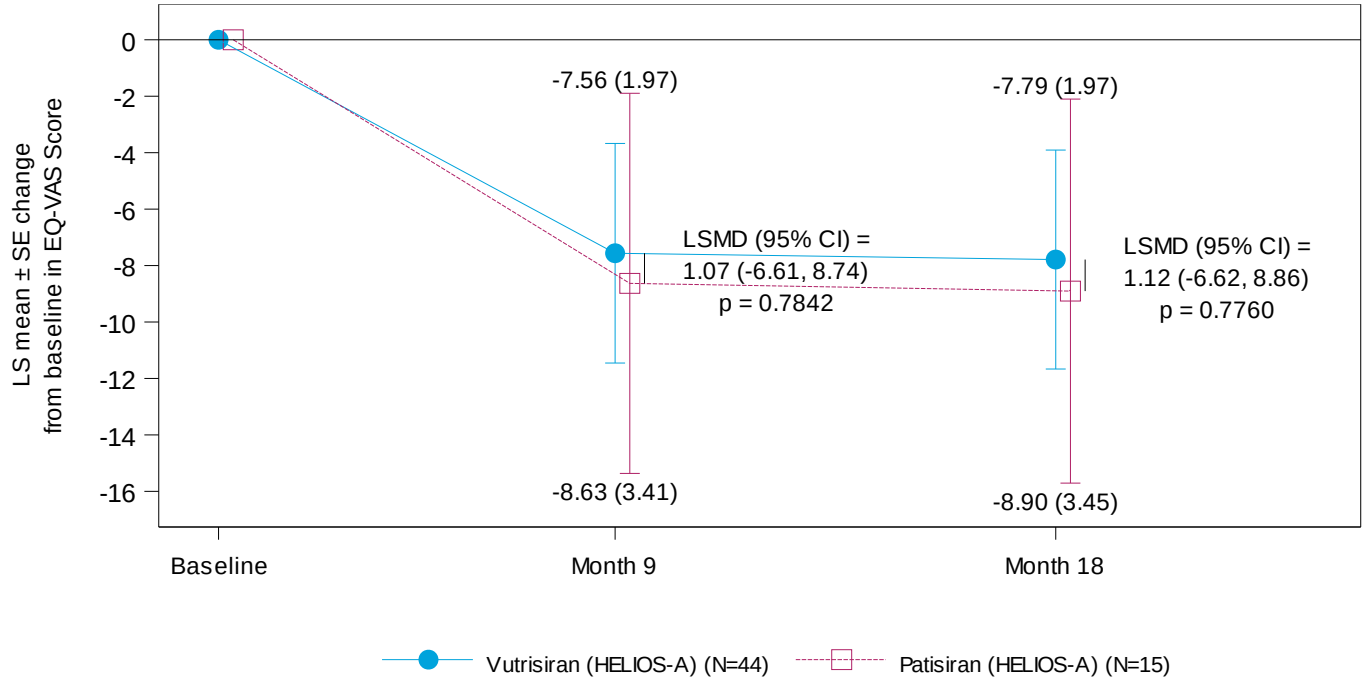
N evaluable			
Vutrisiran	77	76	74
Patisiran	26	25	25

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

Alnylam Pharmaceuticals Inc.
ALN-TTRSC02-002

EuroQol-Visual Analog Scale (EQ-VAS) Score Change from Baseline Over Time Series Plot
Subgroup Analysis: Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A)
mITT Population

Baseline NIS: ≥50



N evaluable			
Vutrisiran	43	38	38
Patisiran	15	13	12

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

Alnylam Pharmaceuticals Inc.
ALN-TTRSC02-002

Table 7.3
EuroQol-Visual Analog Scale (EQ-VAS) Score: Change from Baseline to Month 18, MMRM Model
Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A) Subgroup Analysis
mITT Population

Subgroup Visit	LS Mean (95% CI) Vutrisiran (HELIOS-A) (N=122)	LS Mean (95% CI) Patisiran (HELIOS-A) (N=42)	LS Mean Difference (Vutrisiran-Patisiran) (95% CI), p-value	Standardized Effect Size (95% CI)
Previous Tetramer Stabilizer Use				
Yes	73	31		
Month 9	-0.06 (-3.30, 3.18)	-1.13 (-6.23, 3.98)	1.07 (-4.98, 7.12), 0.7281	0.07 (-0.35, 0.49)
Month 18	-0.41 (-3.67, 2.85)	-1.34 (-6.46, 3.78)	0.93 (-5.14, 7.00), 0.7623	0.07 (-0.36, 0.49)
No	43	8		
Month 9	7.97 (3.86, 12.08)	-4.25 (-13.70, 5.21)	12.22 (1.92, 22.52), 0.0203	0.89 (0.08, 1.69)
Month 18	7.62 (3.54, 11.70)	-4.46 (-13.90, 4.98)	12.08 (1.81, 22.35), 0.0214	0.77 (-0.03, 1.57)
p-value of Treatment*Previous Tetramer Stabilizer Use	0.0527			

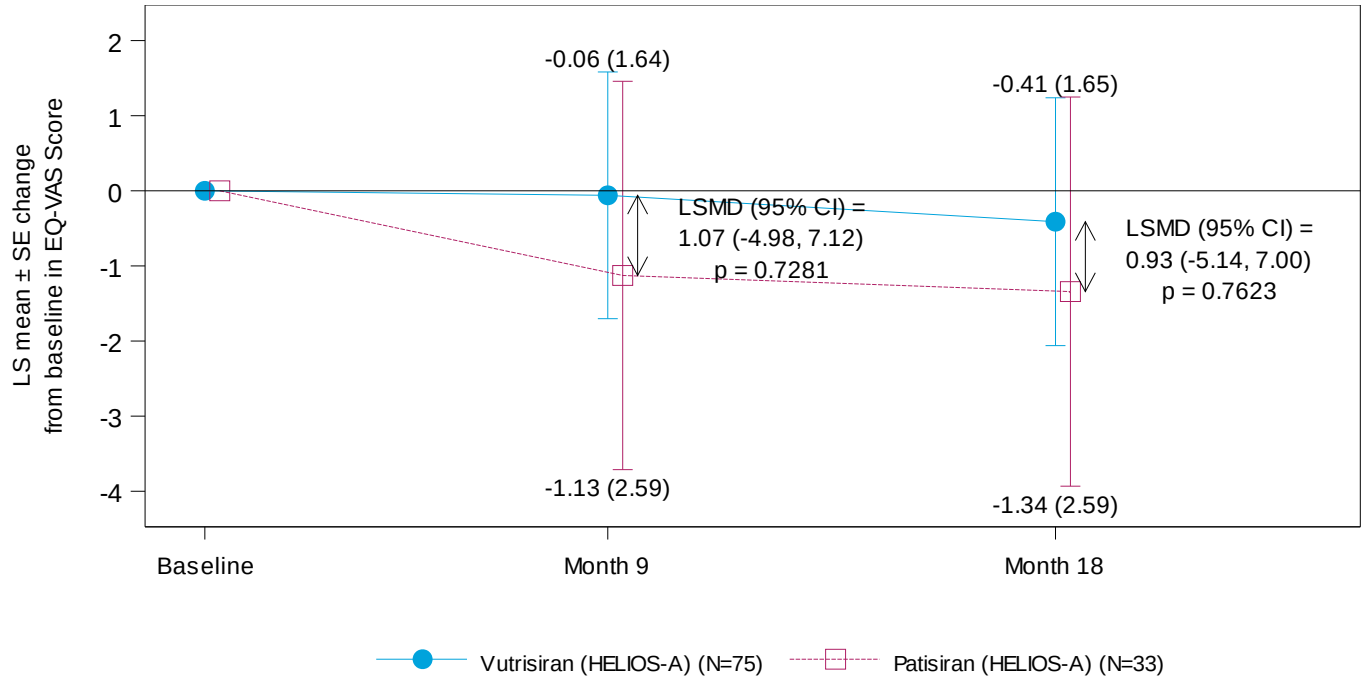
Higher scores indicate higher quality of life (range = 0 to 100). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.
LS estimates and p-value derived from mixed-effects model for repeated measures (MMRM), controlling for categorical factors (treatment, visit), the subgroup variable, continuous covariate (baseline value), and interaction (treatment by visit, treatment by subgroup).
Standardized effect size (d) = LS mean difference/estimated pooled standard deviation with the small sample bias correction.

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

Alnylam Pharmaceuticals Inc.
ALN-TTRSC02-002

EuroQol-Visual Analog Scale (EQ-VAS) Score Change from Baseline Over Time Series Plot
Subgroup Analysis: Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A)
mITT Population

Previous Tetramer Stabilizer Use: Yes



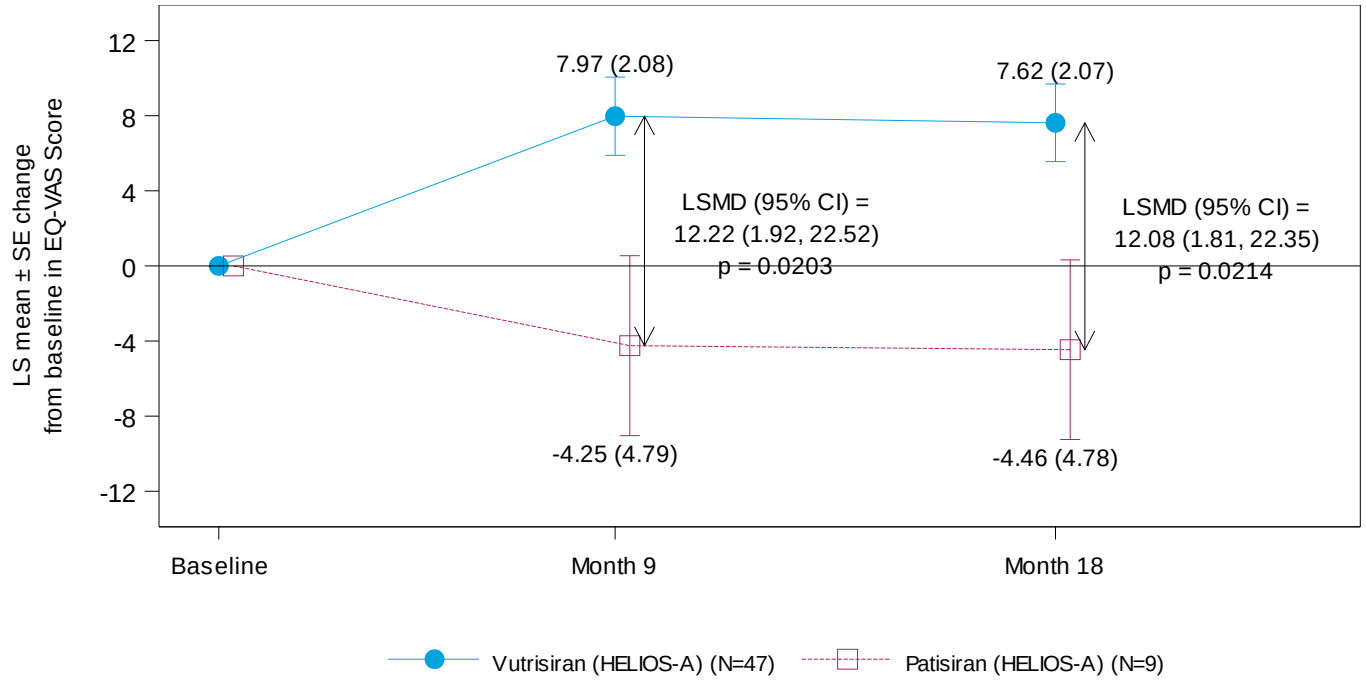
N evaluable			
Vutrisiran	74	73	70
Patisiran	32	31	30

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

Alnylam Pharmaceuticals Inc.
ALN-TTRSC02-002

EuroQol-Visual Analog Scale (EQ-VAS) Score Change from Baseline Over Time Series Plot
Subgroup Analysis: Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A)
mITT Population

Previous Tetramer Stabilizer Use: No



N evaluable			
Vutrisiran	46	41	42
Patisiran	9	7	7

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

Alnylam Pharmaceuticals Inc.
ALN-TTRSC02-002

Table 7.3
EuroQol-Visual Analog Scale (EQ-VAS) Score: Change from Baseline to Month 18, MMRM Model
Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A) Subgroup Analysis
mITT Population

Subgroup Visit	LS Mean (95% CI) Vutrisiran (HELIOS-A) (N=122)	LS Mean (95% CI) Patisiran (HELIOS-A) (N=42)	LS Mean Difference (Vutrisiran-Patisiran) (95% CI), p-value	Standardized Effect Size (95% CI)
Genotype				
V30M	52	20		
Month 9	0.31 (-3.51, 4.12)	-0.73 (-6.97, 5.51)	1.03 (-6.28, 8.35), 0.7805	0.07 (-0.45, 0.59)
Month 18	0.04 (-3.82, 3.90)	-1.01 (-7.27, 5.25)	1.05 (-6.31, 8.40), 0.7791	0.08 (-0.43, 0.59)
non-V30M	64	19		
Month 9	4.93 (1.46, 8.40)	-2.76 (-9.07, 3.54)	7.69 (0.49, 14.89), 0.0364	0.52 (0.01, 1.04)
Month 18	4.66 (1.11, 8.21)	-3.04 (-9.58, 3.50)	7.70 (0.26, 15.14), 0.0425	0.46 (-0.08, 1.00)
p-value of Treatment*Genotype	0.1729			

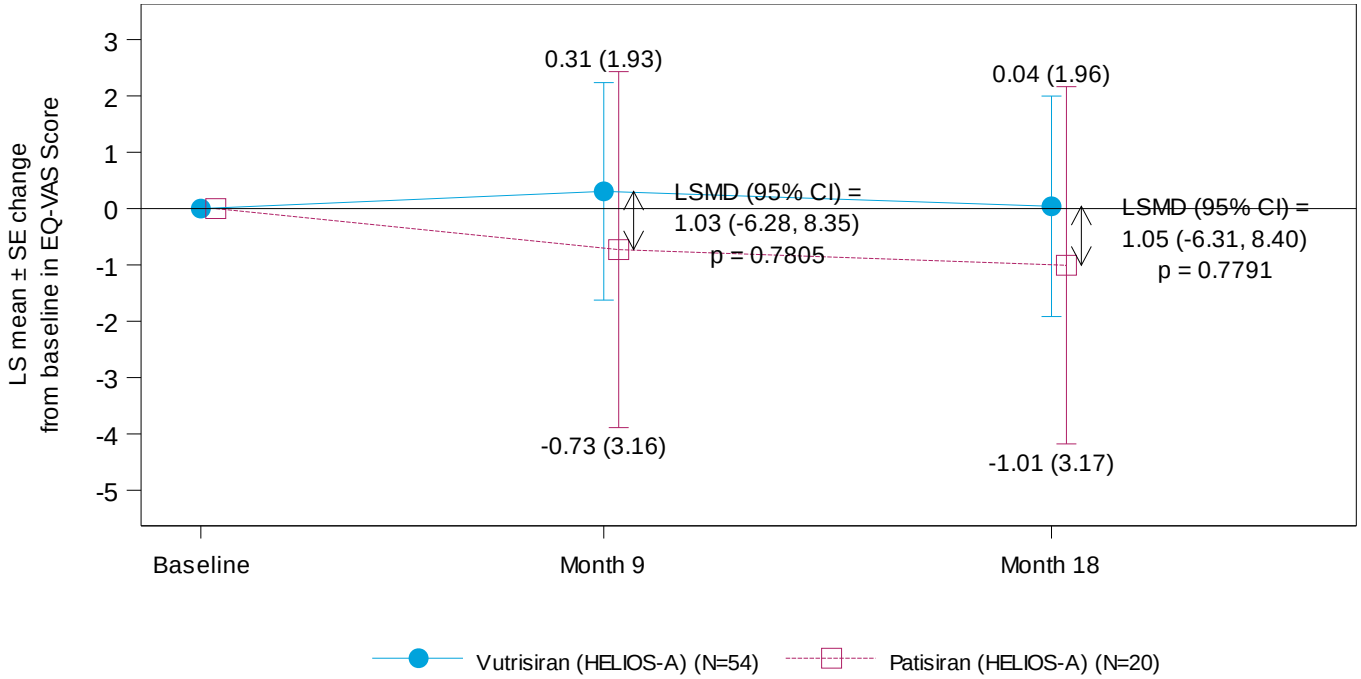
Higher scores indicate higher quality of life (range = 0 to 100). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.
LS estimates and p-value derived from mixed-effects model for repeated measures (MMRM), controlling for categorical factors (treatment, visit), the subgroup variable, continuous covariate (baseline value), and interaction (treatment by visit, treatment by subgroup).
Standardized effect size (d) = LS mean difference/estimated pooled standard deviation with the small sample bias correction.

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

Alnylam Pharmaceuticals Inc.
ALN-TTRSC02-002

EuroQol-Visual Analog Scale (EQ-VAS) Score Change from Baseline Over Time Series Plot
Subgroup Analysis: Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A)
mITT Population

Genotype: V30M



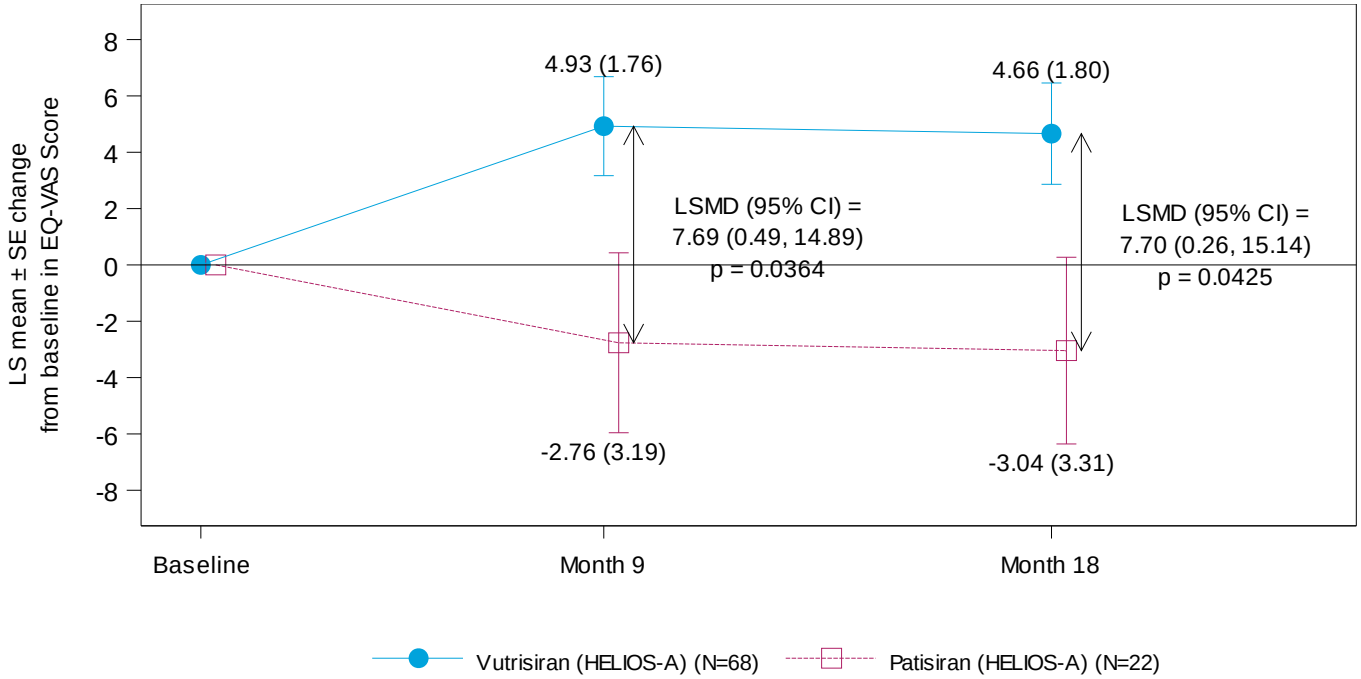
N evaluable			
Vutrisiran	53	51	51
Patisiran	20	19	20

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

Alnylam Pharmaceuticals Inc.
ALN-TTRSC02-002

EuroQol-Visual Analog Scale (EQ-VAS) Score Change from Baseline Over Time Series Plot
Subgroup Analysis: Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A)
mITT Population

Genotype: non-V30M



N evaluable			
Vutrisiran	67	63	61
Patisiran	21	19	17

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

Alnylam Pharmaceuticals Inc.
ALN-TTRSC02-002

Table 7.3
EuroQol-Visual Analog Scale (EQ-VAS) Score: Change from Baseline to Month 18, MMRM Model
Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A) Subgroup Analysis
mITT Population

Subgroup Visit	LS Mean (95% CI) Vutrisiran (HELIOS-A) (N=122)	LS Mean (95% CI) Patisiran (HELIOS-A) (N=42)	LS Mean Difference (Vutrisiran-Patisiran) (95% CI), p-value	Standardized Effect Size (95% CI)
FAP Stage				
I	82	29		
Month 9	5.43 (2.30, 8.56)	-0.45 (-5.71, 4.80)	5.89 (-0.18, 11.95), 0.0570	0.46 (0.03, 0.89)
Month 18	5.14 (1.94, 8.35)	-0.76 (-6.08, 4.55)	5.91 (-0.24, 12.06), 0.0596	0.42 (-0.00, 0.85)
II&III	34	10		
Month 9	-3.11 (-7.75, 1.53)	-5.36 (-13.83, 3.11)	2.25 (-7.25, 11.75), 0.6405	0.12 (-0.57, 0.82)
Month 18	-3.40 (-8.09, 1.29)	-5.67 (-14.40, 3.06)	2.27 (-7.49, 12.04), 0.6466	0.13 (-0.63, 0.89)
p-value of Treatment*FAP Stage	0.5034			

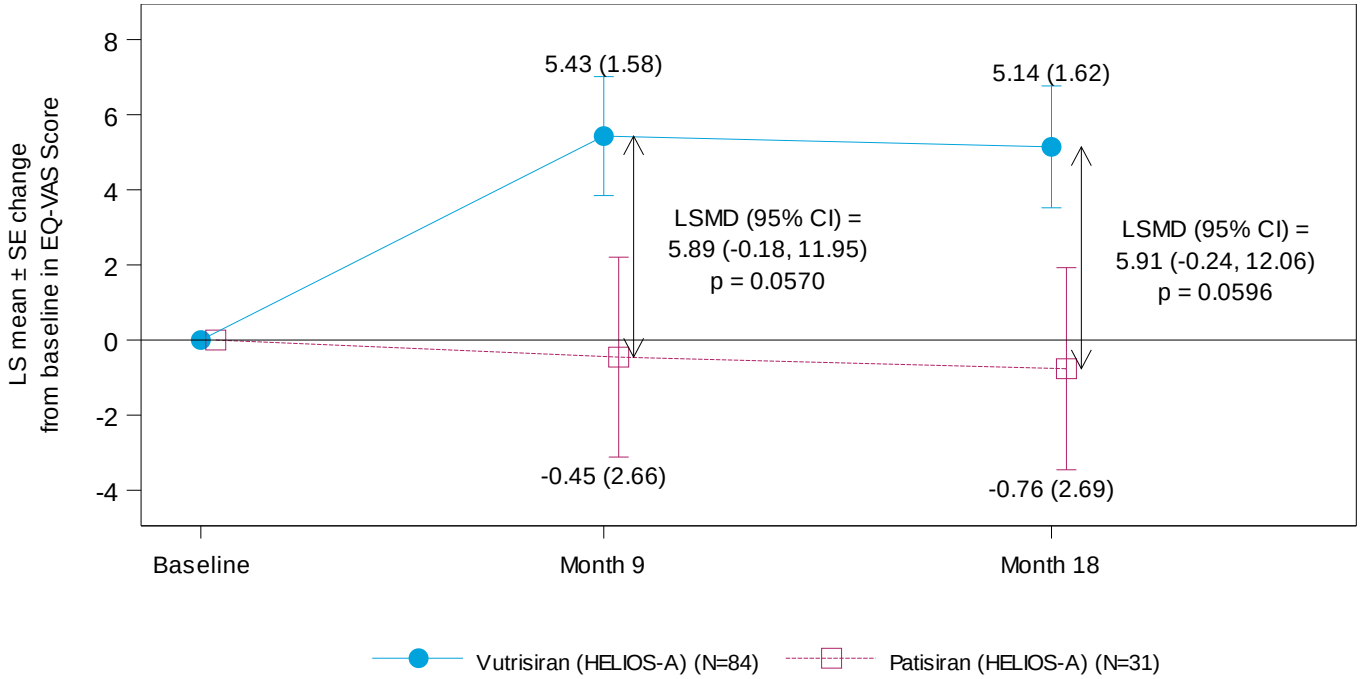
Higher scores indicate higher quality of life (range = 0 to 100). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.
LS estimates and p-value derived from mixed-effects model for repeated measures (MMRM), controlling for categorical factors (treatment, visit), the subgroup variable, continuous covariate (baseline value), and interaction (treatment by visit, treatment by subgroup).
Standardized effect size (d) = LS mean difference/estimated pooled standard deviation with the small sample bias correction.

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

Alnylam Pharmaceuticals Inc.
ALN-TTRSC02-002

EuroQol-Visual Analog Scale (EQ-VAS) Score Change from Baseline Over Time Series Plot
Subgroup Analysis: Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A)
mITT Population

FAP Stage: I



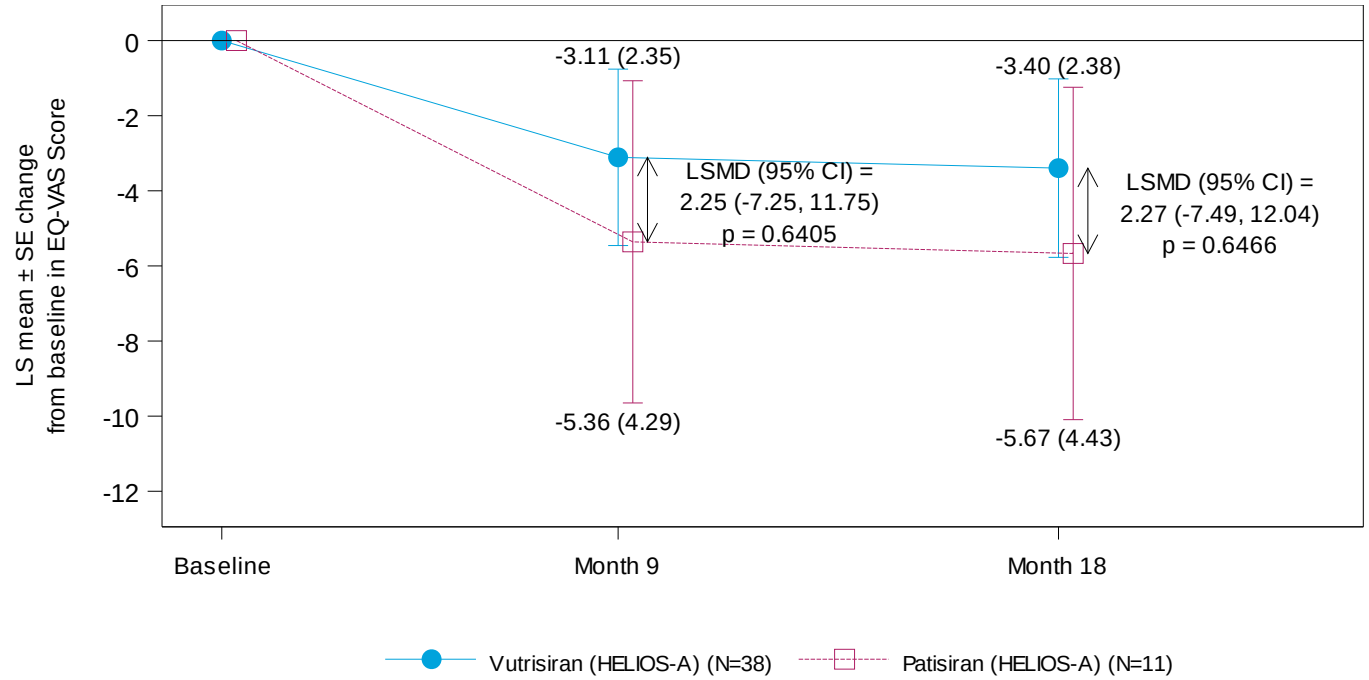
N evaluable			
Vutrisiran	83	81	80
Patisiran	30	28	29

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

Alnylam Pharmaceuticals Inc.
ALN-TTRSC02-002

EuroQol-Visual Analog Scale (EQ-VAS) Score Change from Baseline Over Time Series Plot
Subgroup Analysis: Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A)
mITT Population

FAP Stage: II&III



N evaluable			
Vutrisiran	37	33	32
Patisiran	11	10	8

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

Alnylam Pharmaceuticals Inc.
ALN-TTRSC02-002

Table 7.3
EuroQol-Visual Analog Scale (EQ-VAS) Score: Change from Baseline to Month 18, MMRM Model
Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A) Subgroup Analysis
mITT Population

Subgroup Visit	LS Mean (95% CI) Vutrisiran (HELIOS-A) (N=122)	LS Mean (95% CI) Patisiran (HELIOS-A) (N=42)	LS Mean Difference (Vutrisiran-Patisiran) (95% CI), p-value	Standardized Effect Size (95% CI)
Cardiac Subpopulation				
Yes	37	14		
Month 9	0.32 (-4.13, 4.77)	-4.70 (-12.01, 2.62)	5.02 (-3.53, 13.57), 0.2484	0.36 (-0.25, 0.96)
Month 18	0.04 (-4.42, 4.49)	-4.94 (-12.31, 2.42)	4.98 (-3.62, 13.58), 0.2549	0.32 (-0.31, 0.95)
No	79	25		
Month 9	4.09 (0.86, 7.33)	-0.06 (-5.80, 5.67)	4.16 (-2.41, 10.73), 0.2135	0.27 (-0.19, 0.73)
Month 18	3.81 (0.58, 7.03)	-0.31 (-6.02, 5.40)	4.12 (-2.42, 10.66), 0.2156	0.28 (-0.18, 0.74)
p-value of Treatment*Cardiac Subpopulation	0.8660			

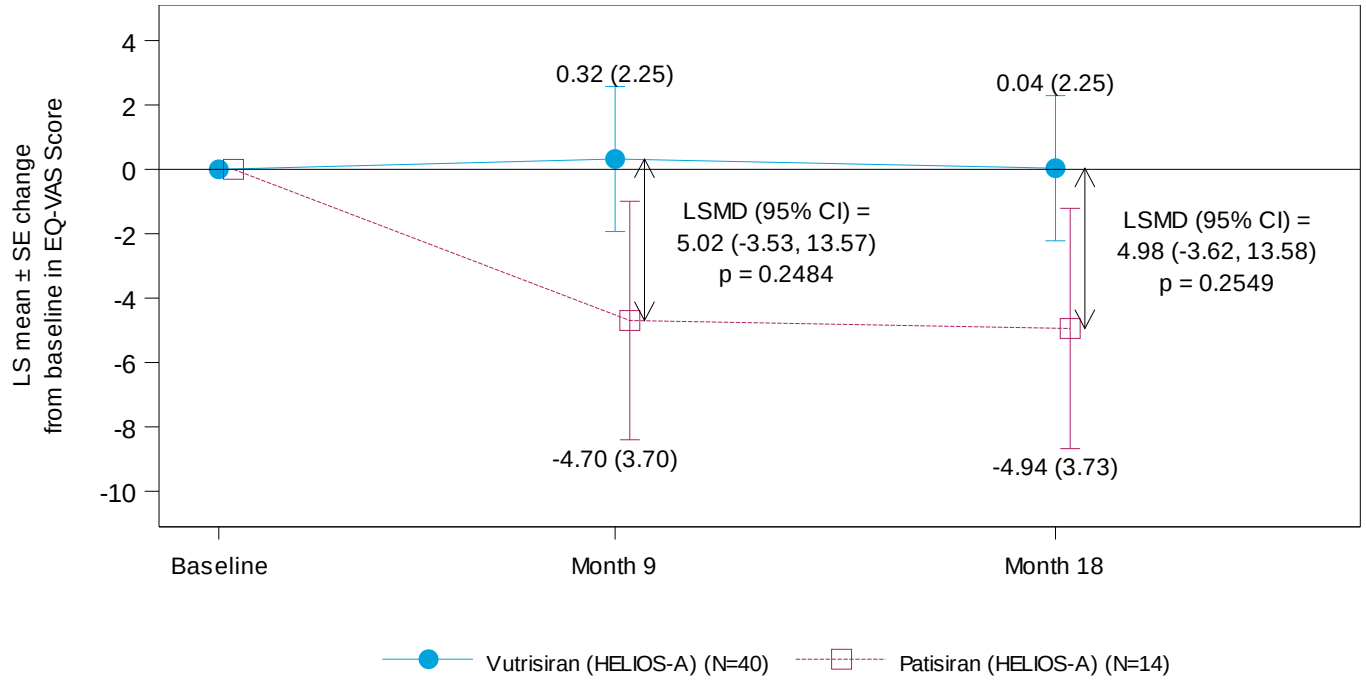
Higher scores indicate higher quality of life (range = 0 to 100). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.
LS estimates and p-value derived from mixed-effects model for repeated measures (MMRM), controlling for categorical factors (treatment, visit), the subgroup variable, continuous covariate (baseline value), and interaction (treatment by visit, treatment by subgroup).
Standardized effect size (d) = LS mean difference/estimated pooled standard deviation with the small sample bias correction.

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

Alnylam Pharmaceuticals Inc.
ALN-TTRSC02-002

EuroQol-Visual Analog Scale (EQ-VAS) Score Change from Baseline Over Time Series Plot
Subgroup Analysis: Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A)
mITT Population

Cardiac Subpopulation: Yes



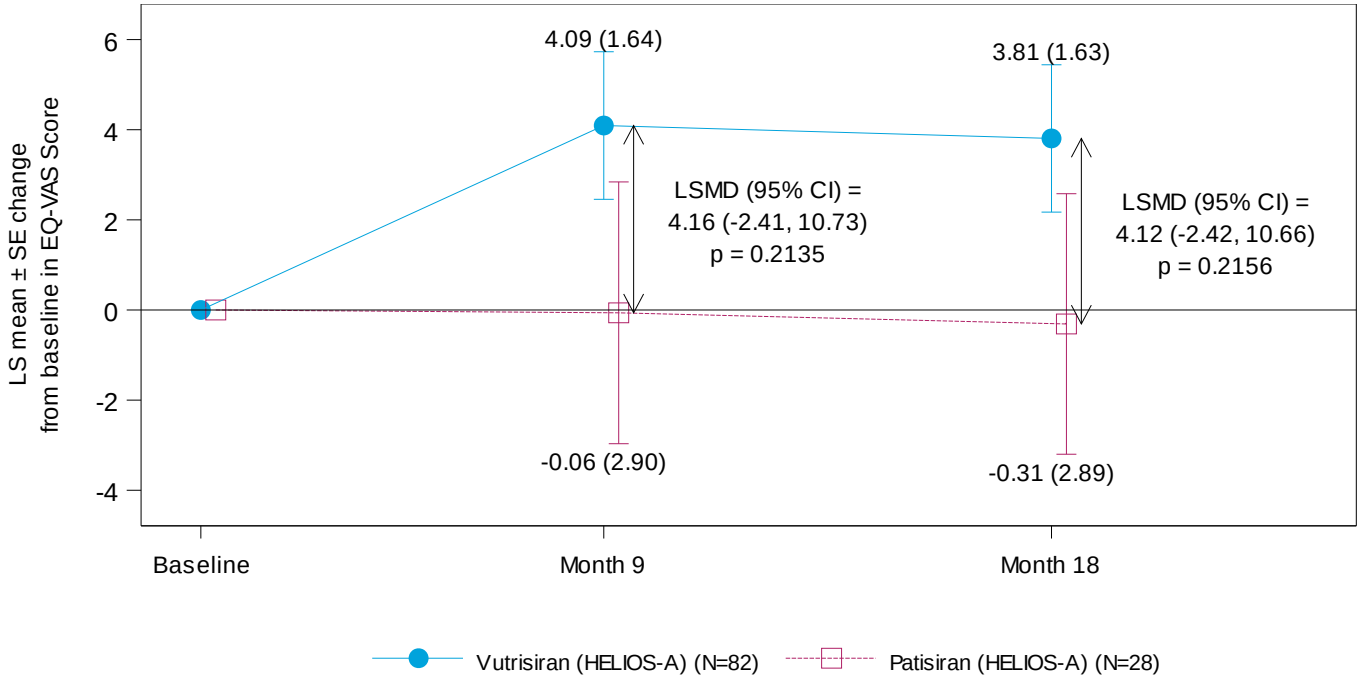
N evaluable			
Vutrisiran	39	37	36
Patisiran	14	14	13

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

Alnylam Pharmaceuticals Inc.
ALN-TTRSC02-002

EuroQol-Visual Analog Scale (EQ-VAS) Score Change from Baseline Over Time Series Plot
Subgroup Analysis: Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A)
mITT Population

Cardiac Subpopulation: No



N evaluable			
Vutrisiran	81	77	76
Patisiran	27	24	24

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

Alnylam Pharmaceuticals Inc.
ALN-TTRSC02-002

Table 7.3
EuroQol-Visual Analog Scale (EQ-VAS) Score: Change from Baseline to Month 18, MMRM Model
Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A) Subgroup Analysis
mITT Population

Subgroup Visit	LS Mean (95% CI) Vutrisiran (HELIOS-A) (N=122)	LS Mean (95% CI) Patisiran (HELIOS-A) (N=42)	LS Mean Difference (Vutrisiran-Patisiran) (95% CI), p-value	Standardized Effect Size (95% CI)
Weight (kg)				
<65	44	14		
Month 9	1.22 (-2.91, 5.36)	-4.68 (-12.07, 2.72)	5.90 (-2.57, 14.37), 0.1710	0.41 (-0.20, 1.03)
Month 18	0.93 (-3.23, 5.09)	-4.81 (-12.11, 2.48)	5.74 (-2.65, 14.13), 0.1787	0.34 (-0.26, 0.94)
≥65	72	25		
Month 9	3.87 (0.52, 7.23)	-0.16 (-5.84, 5.52)	4.04 (-2.56, 10.64), 0.2287	0.26 (-0.19, 0.71)
Month 18	3.58 (0.23, 6.92)	-0.30 (-6.08, 5.48)	3.88 (-2.80, 10.56), 0.2530	0.28 (-0.19, 0.75)
p-value of Treatment*Weight	0.7136			

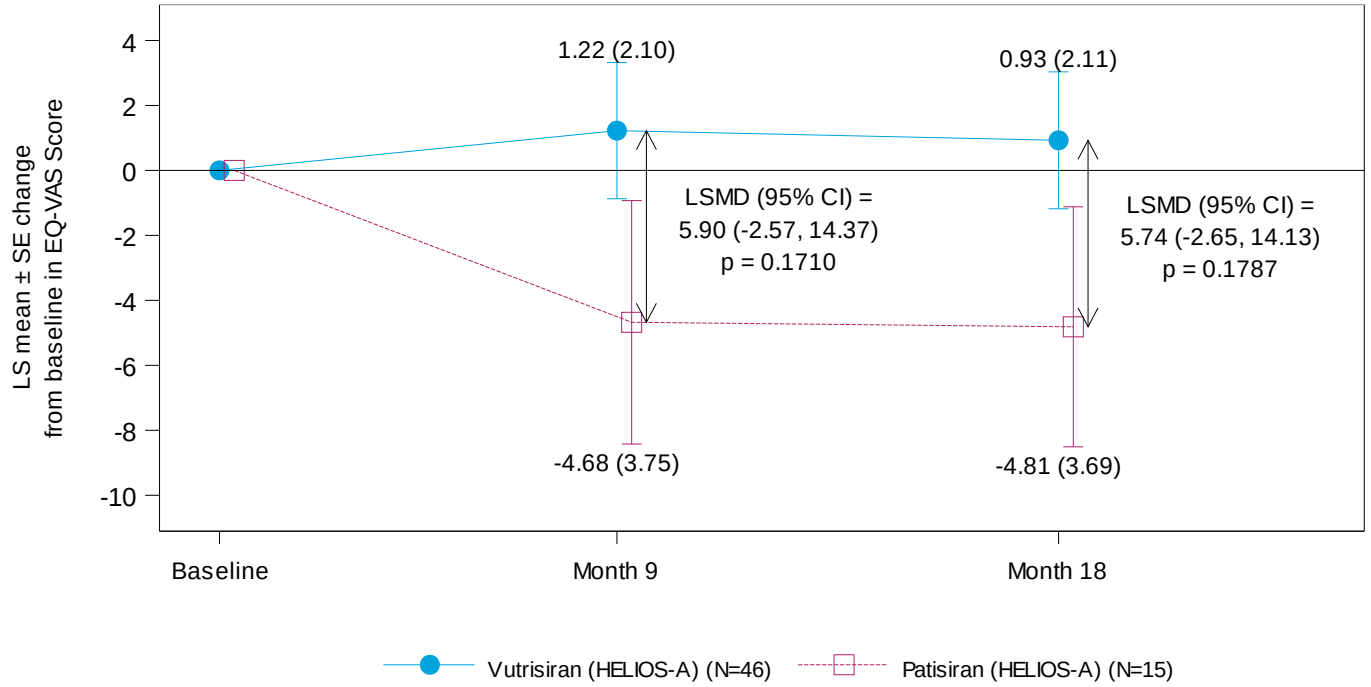
Higher scores indicate higher quality of life (range = 0 to 100). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.
LS estimates and p-value derived from mixed-effects model for repeated measures (MMRM), controlling for categorical factors (treatment, visit), the subgroup variable, continuous covariate (baseline value), and interaction (treatment by visit, treatment by subgroup).
Standardized effect size (d) = LS mean difference/estimated pooled standard deviation with the small sample bias correction.

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

Alnylam Pharmaceuticals Inc.
ALN-TTRSC02-002

EuroQol-Visual Analog Scale (EQ-VAS) Score Change from Baseline Over Time Series Plot
Subgroup Analysis: Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A)
mITT Population

Weight (kg): <65



N evaluable

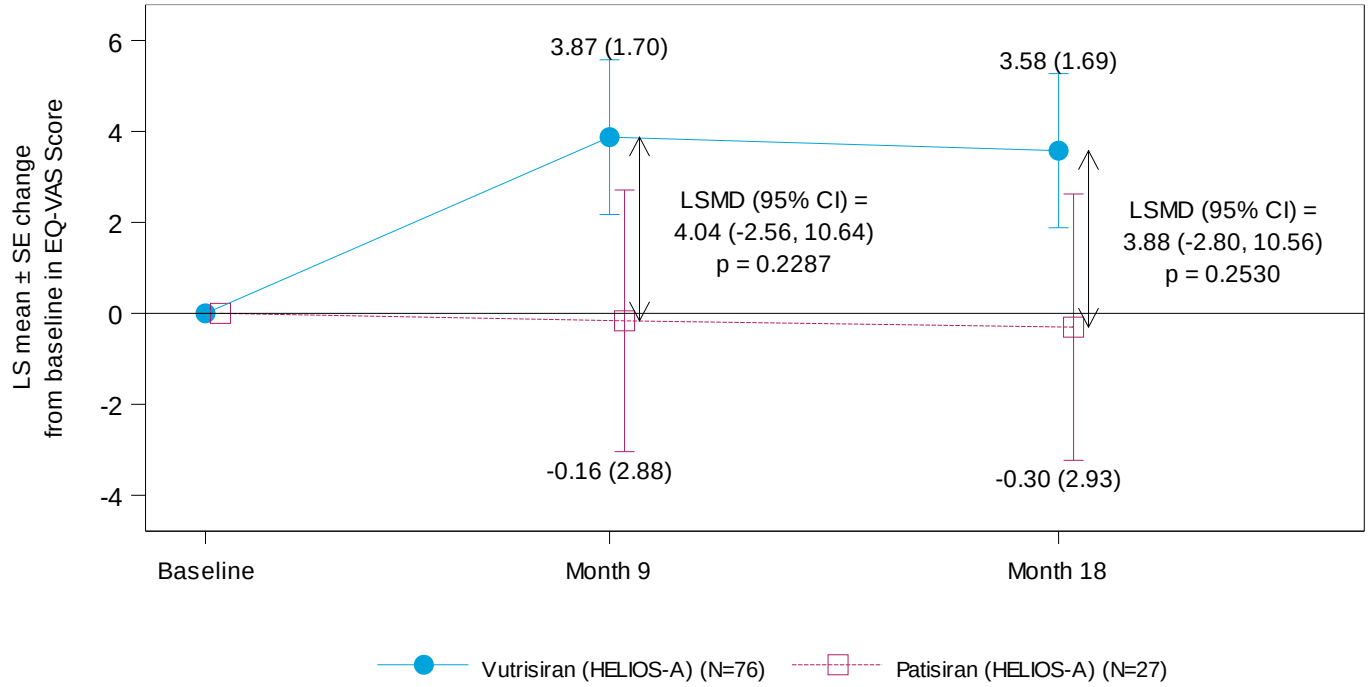
Vutrisiran	46	44	42
Patisiran	14	13	14

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

Alnylam Pharmaceuticals Inc.
ALN-TTRSC02-002

EuroQol-Visual Analog Scale (EQ-VAS) Score Change from Baseline Over Time Series Plot
Subgroup Analysis: Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A)
mITT Population

Weight (kg): ≥65



N evaluable			
Vutrisiran	74	70	70
Patisiran	27	25	23

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

Alnylam Pharmaceuticals Inc.
ALN-TTRSC02-002

Table 7.5
EuroQol-Visual Analog Scale (EQ-VAS) Score: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Age (years): <65

Subgroup Visit	Vutrisiran (HELIOS-A) (N=76)	Patisiran (HELIOS-A) (N=31)
Baseline		
n	75	30
Mean (SD)	66.7 (18.7)	64.5 (16.4)
SE	2.2	3.0
Median	70.0	70.0
Min, Max	25, 99	20, 90
Month 9		
Actual Value		
n	74	29
Mean (SD)	68.2 (18.7)	64.0 (17.7)
SE	2.2	3.3
Median	70.0	70.0
Min, Max	5, 100	25, 90
Change from baseline		
n	73	28
Mean (SD)	1.5 (16.9)	-1.3 (14.2)
SE	2.0	2.7
Median	0.0	0.0
Min, Max	-60, 50	-35, 25

Higher scores indicate higher quality of life (range = 0 to 100). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

Alnylam Pharmaceuticals Inc.
ALN-TTRSC02-002

Table 7.5
EuroQol-Visual Analog Scale (EQ-VAS) Score: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Age (years): <65

Subgroup Visit	Vutrisiran (HELIOS-A) (N=76)	Patisiran (HELIOS-A) (N=31)
Month 18		
Actual Value		
n	74	28
Mean (SD)	68.8 (18.5)	62.9 (15.5)
SE	2.1	2.9
Median	70.0	62.5
Min, Max	25, 100	30, 100
Change from baseline		
n	73	28
Mean (SD)	1.8 (16.8)	-3.9 (14.8)
SE	2.0	2.8
Median	0.0	0.0
Min, Max	-50, 50	-40, 20

Higher scores indicate higher quality of life (range = 0 to 100). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

Alnylam Pharmaceuticals Inc.
ALN-TTRSC02-002

Table 7.5
EuroQol-Visual Analog Scale (EQ-VAS) Score: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Age (years): ≥65

Subgroup Visit	Vutrisiran (HELIOS-A) (N=46)	Patisiran (HELIOS-A) (N=11)
Baseline		
n	45	11
Mean (SD)	61.0 (17.8)	59.1 (15.3)
SE	2.7	4.6
Median	60.0	60.0
Min, Max	15, 95	40, 90
Month 9		
Actual Value		
n	41	10
Mean (SD)	67.1 (18.4)	58.0 (18.4)
SE	2.9	5.8
Median	70.0	60.0
Min, Max	25, 100	25, 80
Change from baseline		
n	41	10
Mean (SD)	4.1 (18.1)	-2.0 (13.4)
SE	2.8	4.2
Median	0.0	-2.5
Min, Max	-35, 55	-25, 15

Higher scores indicate higher quality of life (range = 0 to 100). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

Alnylam Pharmaceuticals Inc.
ALN-TTRSC02-002

Table 7.5
EuroQol-Visual Analog Scale (EQ-VAS) Score: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Age (years): ≥65

Subgroup Visit	Vutrisiran (HELIOS-A) (N=46)	Patisiran (HELIOS-A) (N=11)
Month 18		
Actual Value		
n	40	9
Mean (SD)	65.0 (17.5)	63.8 (15.4)
SE	2.8	5.1
Median	62.5	70.0
Min, Max	30, 95	40, 80
Change from baseline		
n	39	9
Mean (SD)	1.7 (18.8)	1.6 (17.6)
SE	3.0	5.9
Median	5.0	10.0
Min, Max	-40, 40	-25, 25

Higher scores indicate higher quality of life (range = 0 to 100). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

Alnylam Pharmaceuticals Inc.
ALN-TTRSC02-002

Table 7.5
EuroQol-Visual Analog Scale (EQ-VAS) Score: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Sex: Male

Subgroup Visit	Vutrisiran (HELIOS-A) (N=79)	Patisiran (HELIOS-A) (N=27)
Baseline		
n	78	27
Mean (SD)	63.4 (18.3)	61.3 (16.7)
SE	2.1	3.2
Median	65.0	65.0
Min, Max	25, 95	20, 90
Month 9		
Actual Value		
n	75	25
Mean (SD)	65.2 (17.5)	62.6 (17.0)
SE	2.0	3.4
Median	70.0	70.0
Min, Max	25, 100	25, 85
Change from baseline		
n	75	25
Mean (SD)	1.1 (15.9)	0.2 (13.1)
SE	1.8	2.6
Median	0.0	0.0
Min, Max	-40, 40	-35, 25

Higher scores indicate higher quality of life (range = 0 to 100). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

Alnylam Pharmaceuticals Inc.
ALN-TTRSC02-002

Table 7.5
EuroQol-Visual Analog Scale (EQ-VAS) Score: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Sex: Male

Subgroup Visit	Vutrisiran (HELIOS-A) (N=79)	Patisiran (HELIOS-A) (N=27)
Month 18		
Actual Value		
n	74	23
Mean (SD)	65.9 (16.7)	62.8 (13.0)
SE	1.9	2.7
Median	70.0	65.0
Min, Max	25, 100	35, 85
Change from baseline		
n	73	23
Mean (SD)	1.3 (18.1)	-2.4 (15.5)
SE	2.1	3.2
Median	0.0	0.0
Min, Max	-50, 50	-40, 20

Higher scores indicate higher quality of life (range = 0 to 100). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

Alnylam Pharmaceuticals Inc.
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Table 7.5
EuroQol-Visual Analog Scale (EQ-VAS) Score: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Sex: Female

Subgroup Visit	Vutrisiran (HELIOS-A) (N=43)	Patisiran (HELIOS-A) (N=15)
Baseline		
n	42	14
Mean (SD)	66.5 (19.0)	66.4 (15.0)
SE	2.9	4.0
Median	67.5	65.0
Min, Max	15, 99	45, 90
Month 9		
Actual Value		
n	40	14
Mean (SD)	72.7 (19.6)	62.1 (20.0)
SE	3.1	5.3
Median	80.0	62.5
Min, Max	5, 100	25, 90
Change from baseline		
n	39	13
Mean (SD)	4.9 (19.8)	-4.6 (15.1)
SE	3.2	4.2
Median	5.0	-10.0
Min, Max	-60, 55	-25, 20

Higher scores indicate higher quality of life (range = 0 to 100). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

Alnylam Pharmaceuticals Inc.
ALN-TTRSC02-002

Table 7.5
EuroQol-Visual Analog Scale (EQ-VAS) Score: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Sex: Female

Subgroup Visit	Vutrisiran (HELIOS-A) (N=43)	Patisiran (HELIOS-A) (N=15)
Month 18		
Actual Value		
n	40	14
Mean (SD)	70.3 (20.5)	63.7 (19.0)
SE	3.2	5.1
Median	75.0	60.0
Min, Max	30, 100	30, 100
Change from baseline		
n	39	14
Mean (SD)	2.8 (16.2)	-2.7 (15.9)
SE	2.6	4.3
Median	5.0	-2.5
Min, Max	-35, 50	-25, 25

Higher scores indicate higher quality of life (range = 0 to 100). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

Alnylam Pharmaceuticals Inc.
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Table 7.5
EuroQol-Visual Analog Scale (EQ-VAS) Score: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Race: White

Subgroup Visit	Vutrisiran (HELIOS-A) (N=86)	Patisiran (HELIOS-A) (N=29)
Baseline		
n	84	28
Mean (SD)	63.2 (19.3)	62.1 (16.4)
SE	2.1	3.1
Median	66.0	65.0
Min, Max	15, 99	20, 90
Month 9		
Actual Value		
n	81	27
Mean (SD)	65.8 (18.4)	59.6 (18.0)
SE	2.0	3.5
Median	70.0	65.0
Min, Max	5, 100	25, 80
Change from baseline		
n	80	26
Mean (SD)	1.2 (16.2)	-3.1 (11.6)
SE	1.8	2.3
Median	0.0	-5.0
Min, Max	-60, 55	-25, 20

Higher scores indicate higher quality of life (range = 0 to 100). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

Alnylam Pharmaceuticals Inc.
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Table 7.5
EuroQol-Visual Analog Scale (EQ-VAS) Score: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Race: White

Subgroup Visit	Vutrisiran (HELIOS-A) (N=86)	Patisiran (HELIOS-A) (N=29)
Month 18		
Actual Value		
n	81	26
Mean (SD)	65.9 (17.7)	63.5 (16.1)
SE	2.0	3.2
Median	70.0	65.0
Min, Max	25, 100	30, 100
Change from baseline		
n	79	26
Mean (SD)	1.5 (15.2)	-0.7 (14.2)
SE	1.7	2.8
Median	0.0	0.0
Min, Max	-40, 50	-25, 25

Higher scores indicate higher quality of life (range = 0 to 100). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

Alnylam Pharmaceuticals Inc.
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Table 7.5
EuroQol-Visual Analog Scale (EQ-VAS) Score: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Race: All Other Races

Subgroup Visit	Vutrisiran (HELIOS-A) (N=36)	Patisiran (HELIOS-A) (N=13)
Baseline		
n	36	13
Mean (SD)	67.6 (16.4)	65.0 (15.9)
SE	2.7	4.4
Median	65.0	70.0
Min, Max	25, 95	40, 90
Month 9		
Actual Value		
n	34	12
Mean (SD)	72.6 (18.1)	68.8 (16.4)
SE	3.1	4.7
Median	80.0	67.5
Min, Max	25, 100	40, 90
Change from baseline		
n	34	12
Mean (SD)	5.2 (19.7)	2.1 (17.8)
SE	3.4	5.1
Median	5.0	7.5
Min, Max	-40, 50	-35, 25

Higher scores indicate higher quality of life (range = 0 to 100). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

Alnylam Pharmaceuticals Inc.
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Table 7.5
EuroQol-Visual Analog Scale (EQ-VAS) Score: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Race: All Other Races

Subgroup Visit	Vutrisiran (HELIOS-A) (N=36)	Patisiran (HELIOS-A) (N=13)
Month 18		
Actual Value		
n	33	11
Mean (SD)	71.3 (18.9)	62.3 (13.8)
SE	3.3	4.2
Median	75.0	60.0
Min, Max	30, 100	35, 85
Change from baseline		
n	33	11
Mean (SD)	2.4 (22.0)	-6.8 (18.1)
SE	3.8	5.4
Median	0.0	-5.0
Min, Max	-50, 50	-40, 20

Higher scores indicate higher quality of life (range = 0 to 100). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

Alnylam Pharmaceuticals Inc.
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Table 7.5
EuroQol-Visual Analog Scale (EQ-VAS) Score: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Region: North America

Subgroup Visit	Vutrisiran (HELIOS-A) (N=27)	Patisiran (HELIOS-A) (N=8)
Baseline		
n	26	8
Mean (SD)	67.8 (18.5)	67.5 (14.6)
SE	3.6	5.2
Median	70.0	70.0
Min, Max	25, 99	40, 90
Month 9		
Actual Value		
n	25	8
Mean (SD)	78.0 (13.1)	66.9 (11.3)
SE	2.6	4.0
Median	75.0	67.5
Min, Max	60, 100	50, 80
Change from baseline		
n	24	8
Mean (SD)	9.9 (15.2)	-0.6 (10.8)
SE	3.1	3.8
Median	7.5	0.0
Min, Max	-16, 40	-15, 15

Higher scores indicate higher quality of life (range = 0 to 100). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

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Table 7.5
EuroQol-Visual Analog Scale (EQ-VAS) Score: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Region: North America

Subgroup Visit	Vutrisiran (HELIOS-A) (N=27)	Patisiran (HELIOS-A) (N=8)
Month 18		
Actual Value		
n	25	7
Mean (SD)	78.4 (10.9)	68.6 (16.0)
SE	2.2	6.0
Median	80.0	65.0
Min, Max	60, 100	50, 100
Change from baseline		
n	24	7
Mean (SD)	9.9 (17.4)	-2.9 (13.2)
SE	3.5	5.0
Median	5.0	0.0
Min, Max	-21, 50	-25, 10

Higher scores indicate higher quality of life (range = 0 to 100). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

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Table 7.5
EuroQol-Visual Analog Scale (EQ-VAS) Score: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Region: Western Europe

Subgroup Visit	Vutrisiran (HELIOS-A) (N=42)	Patisiran (HELIOS-A) (N=20)
Baseline		
n	41	19
Mean (SD)	62.0 (20.3)	63.7 (12.2)
SE	3.2	2.8
Median	65.0	65.0
Min, Max	15, 95	45, 90
Month 9		
Actual Value		
n	38	18
Mean (SD)	63.8 (17.4)	63.3 (15.9)
SE	2.8	3.7
Median	67.5	70.0
Min, Max	25, 95	25, 80
Change from baseline		
n	38	17
Mean (SD)	-0.2 (15.7)	-1.5 (13.6)
SE	2.5	3.3
Median	0.0	-5.0
Min, Max	-32, 55	-25, 20

Higher scores indicate higher quality of life (range = 0 to 100). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

Alnylam Pharmaceuticals Inc.
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Table 7.5
EuroQol-Visual Analog Scale (EQ-VAS) Score: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Region: Western Europe

Subgroup Visit	Vutrisiran (HELIOS-A) (N=42)	Patisiran (HELIOS-A) (N=20)
Month 18		
Actual Value		
n	39	17
Mean (SD)	62.3 (18.8)	65.6 (13.5)
SE	3.0	3.3
Median	60.0	65.0
Min, Max	30, 95	40, 85
Change from baseline		
n	38	17
Mean (SD)	-1.6 (16.1)	0.1 (14.5)
SE	2.6	3.5
Median	0.0	0.0
Min, Max	-40, 25	-25, 25

Higher scores indicate higher quality of life (range = 0 to 100). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

Alnylam Pharmaceuticals Inc.
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Table 7.5
EuroQol-Visual Analog Scale (EQ-VAS) Score: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Region: Rest of World

Subgroup Visit	Vutrisiran (HELIOS-A) (N=53)	Patisiran (HELIOS-A) (N=14)
Baseline		
n	53	14
Mean (SD)	64.8 (17.1)	59.6 (21.3)
SE	2.3	5.7
Median	65.0	65.0
Min, Max	25, 95	20, 90
Month 9		
Actual Value		
n	52	13
Mean (SD)	65.9 (19.9)	58.5 (23.3)
SE	2.8	6.5
Median	70.0	60.0
Min, Max	5, 100	25, 90
Change from baseline		
n	52	13
Mean (SD)	0.9 (18.7)	-1.9 (16.5)
SE	2.6	4.6
Median	0.0	0.0
Min, Max	-60, 50	-35, 25

Higher scores indicate higher quality of life (range = 0 to 100). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

Alnylam Pharmaceuticals Inc.
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Table 7.5
EuroQol-Visual Analog Scale (EQ-VAS) Score: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Region: Rest of World

Subgroup Visit	Vutrisiran (HELIOS-A) (N=53)	Patisiran (HELIOS-A) (N=14)
Month 18		
Actual Value		
n	50	13
Mean (SD)	66.1 (18.5)	56.9 (16.1)
SE	2.6	4.5
Median	70.0	60.0
Min, Max	25, 100	30, 85
Change from baseline		
n	50	13
Mean (SD)	0.5 (17.5)	-5.8 (18.1)
SE	2.5	5.0
Median	0.0	-5.0
Min, Max	-50, 50	-40, 20

Higher scores indicate higher quality of life (range = 0 to 100). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

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Table 7.5
EuroQol-Visual Analog Scale (EQ-VAS) Score: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Baseline NIS: <50

Subgroup Visit	Vutrisiran (HELIOS-A) (N=78)	Patisiran (HELIOS-A) (N=27)
Baseline		
n	77	26
Mean (SD)	69.1 (17.2)	69.0 (12.6)
SE	2.0	2.5
Median	70.0	70.0
Min, Max	25, 99	40, 90
Month 9		
Actual Value		
n	77	26
Mean (SD)	74.7 (15.0)	69.6 (13.0)
SE	1.7	2.6
Median	75.0	70.0
Min, Max	30, 100	40, 90
Change from baseline		
n	76	25
Mean (SD)	5.5 (15.1)	0.6 (13.9)
SE	1.7	2.8
Median	5.0	0.0
Min, Max	-32, 50	-35, 25

Higher scores indicate higher quality of life (range = 0 to 100). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

Alnylam Pharmaceuticals Inc.
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Table 7.5
EuroQol-Visual Analog Scale (EQ-VAS) Score: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Baseline NIS: <50

Subgroup Visit	Vutrisiran (HELIOS-A) (N=78)	Patisiran (HELIOS-A) (N=27)
Month 18		
Actual Value		
n	75	25
Mean (SD)	74.7 (15.2)	67.0 (15.9)
SE	1.8	3.2
Median	75.0	70.0
Min, Max	30, 100	30, 100
Change from baseline		
n	74	25
Mean (SD)	5.2 (16.0)	-3.2 (15.4)
SE	1.9	3.1
Median	4.0	0.0
Min, Max	-35, 50	-40, 20

Higher scores indicate higher quality of life (range = 0 to 100). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

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Table 7.5
EuroQol-Visual Analog Scale (EQ-VAS) Score: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Baseline NIS: ≥50

Subgroup Visit	Vutrisiran (HELIOS-A) (N=44)	Patisiran (HELIOS-A) (N=15)
Baseline		
n	43	15
Mean (SD)	56.4 (18.2)	52.7 (16.7)
SE	2.8	4.3
Median	55.0	50.0
Min, Max	15, 90	20, 80
Month 9		
Actual Value		
n	38	13
Mean (SD)	53.8 (17.1)	48.1 (17.9)
SE	2.8	5.0
Median	52.5	50.0
Min, Max	5, 85	25, 80
Change from baseline		
n	38	13
Mean (SD)	-3.7 (20.0)	-5.4 (13.1)
SE	3.2	3.6
Median	-5.0	-5.0
Min, Max	-60, 55	-25, 20

Higher scores indicate higher quality of life (range = 0 to 100). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

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Table 7.5
EuroQol-Visual Analog Scale (EQ-VAS) Score: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Baseline NIS: ≥50

Subgroup Visit	Vutrisiran (HELIOS-A) (N=44)	Patisiran (HELIOS-A) (N=15)
Month 18		
Actual Value		
n	39	12
Mean (SD)	53.6 (15.1)	55.0 (10.4)
SE	2.4	3.0
Median	50.0	57.5
Min, Max	25, 80	40, 75
Change from baseline		
n	38	12
Mean (SD)	-4.9 (18.4)	-1.3 (16.3)
SE	3.0	4.7
Median	-5.0	-2.5
Min, Max	-50, 35	-25, 25

Higher scores indicate higher quality of life (range = 0 to 100). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

Alnylam Pharmaceuticals Inc.
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Table 7.5
EuroQol-Visual Analog Scale (EQ-VAS) Score: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Previous Tetramer Stabilizer Use: Yes

Subgroup Visit	Vutrisiran (HELIOS-A) (N=75)	Patisiran (HELIOS-A) (N=33)
Baseline		
n	74	32
Mean (SD)	64.3 (18.8)	62.7 (16.5)
SE	2.2	2.9
Median	66.0	65.0
Min, Max	15, 95	20, 90
Month 9		
Actual Value		
n	73	32
Mean (SD)	64.5 (18.7)	61.6 (18.2)
SE	2.2	3.2
Median	67.0	67.5
Min, Max	5, 100	25, 90
Change from baseline		
n	73	31
Mean (SD)	-0.3 (17.9)	-1.3 (13.2)
SE	2.1	2.4
Median	0.0	-5.0
Min, Max	-60, 55	-25, 25

Higher scores indicate higher quality of life (range = 0 to 100). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

Alnylam Pharmaceuticals Inc.
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Table 7.5
EuroQol-Visual Analog Scale (EQ-VAS) Score: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Previous Tetramer Stabilizer Use: Yes

Subgroup Visit	Vutrisiran (HELIOS-A) (N=75)	Patisiran (HELIOS-A) (N=33)
Month 18		
Actual Value		
n	71	30
Mean (SD)	64.2 (18.2)	63.9 (14.2)
SE	2.2	2.6
Median	70.0	62.5
Min, Max	25, 95	40, 100
Change from baseline		
n	70	30
Mean (SD)	-1.0 (16.6)	-0.8 (14.9)
SE	2.0	2.7
Median	0.0	0.0
Min, Max	-50, 50	-30, 25

Higher scores indicate higher quality of life (range = 0 to 100). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

Alnylam Pharmaceuticals Inc.
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Table 7.5
EuroQol-Visual Analog Scale (EQ-VAS) Score: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Previous Tetramer Stabilizer Use: No

Subgroup Visit	Vutrisiran (HELIOS-A) (N=47)	Patisiran (HELIOS-A) (N=9)
Baseline		
n	46	9
Mean (SD)	64.9 (18.2)	64.4 (15.7)
SE	2.7	5.2
Median	65.0	70.0
Min, Max	25, 99	40, 90
Month 9		
Actual Value		
n	42	7
Mean (SD)	73.6 (16.8)	66.4 (16.8)
SE	2.6	6.3
Median	77.5	65.0
Min, Max	30, 100	40, 90
Change from baseline		
n	41	7
Mean (SD)	7.2 (15.3)	-2.1 (17.3)
SE	2.4	6.5
Median	5.0	5.0
Min, Max	-20, 50	-35, 15

Higher scores indicate higher quality of life (range = 0 to 100). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

Alnylam Pharmaceuticals Inc.
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Table 7.5
EuroQol-Visual Analog Scale (EQ-VAS) Score: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Previous Tetramer Stabilizer Use: No

Subgroup Visit	Vutrisiran (HELIOS-A) (N=47)	Patisiran (HELIOS-A) (N=9)
Month 18		
Actual Value		
n	43	7
Mean (SD)	72.9 (16.9)	60.0 (20.4)
SE	2.6	7.7
Median	70.0	65.0
Min, Max	30, 100	30, 85
Change from baseline		
n	42	7
Mean (SD)	6.4 (18.0)	-10.0 (16.8)
SE	2.8	6.4
Median	7.5	-5.0
Min, Max	-35, 50	-40, 10

Higher scores indicate higher quality of life (range = 0 to 100). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

Alnylam Pharmaceuticals Inc.
ALN-TTRSC02-002

Table 7.5
EuroQol-Visual Analog Scale (EQ-VAS) Score: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Genotype: V30M

Subgroup Visit	Vutrisiran (HELIOS-A) (N=54)	Patisiran (HELIOS-A) (N=20)
Baseline		
n	53	20
Mean (SD)	65.8 (17.3)	63.3 (11.4)
SE	2.4	2.5
Median	65.0	65.0
Min, Max	30, 99	40, 80
Month 9		
Actual Value		
n	51	19
Mean (SD)	63.9 (19.2)	64.2 (16.6)
SE	2.7	3.8
Median	65.0	70.0
Min, Max	5, 95	25, 90
Change from baseline		
n	51	19
Mean (SD)	-2.3 (15.4)	0.3 (14.0)
SE	2.2	3.2
Median	0.0	0.0
Min, Max	-60, 40	-25, 20

Higher scores indicate higher quality of life (range = 0 to 100). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

Alnylam Pharmaceuticals Inc.
ALN-TTRSC02-002

Table 7.5
EuroQol-Visual Analog Scale (EQ-VAS) Score: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Genotype: V30M

Subgroup Visit	Vutrisiran (HELIOS-A) (N=54)	Patisiran (HELIOS-A) (N=20)
Month 18		
Actual Value		
n	52	20
Mean (SD)	67.7 (16.8)	62.4 (14.3)
SE	2.3	3.2
Median	70.0	65.0
Min, Max	30, 100	30, 85
Change from baseline		
n	51	20
Mean (SD)	1.1 (14.0)	-0.9 (15.0)
SE	2.0	3.4
Median	0.0	0.0
Min, Max	-40, 30	-25, 25

Higher scores indicate higher quality of life (range = 0 to 100). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

Alnylam Pharmaceuticals Inc.
ALN-TTRSC02-002

Table 7.5
EuroQol-Visual Analog Scale (EQ-VAS) Score: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Genotype: non-V30M

Subgroup Visit	Vutrisiran (HELIOS-A) (N=68)	Patisiran (HELIOS-A) (N=22)
Baseline		
n	67	21
Mean (SD)	63.5 (19.5)	62.9 (19.9)
SE	2.4	4.3
Median	65.0	70.0
Min, Max	15, 95	20, 90
Month 9		
Actual Value		
n	64	20
Mean (SD)	71.0 (17.4)	60.8 (19.2)
SE	2.2	4.3
Median	70.0	62.5
Min, Max	30, 100	25, 90
Change from baseline		
n	63	19
Mean (SD)	6.3 (18.0)	-3.2 (13.8)
SE	2.3	3.2
Median	5.0	0.0
Min, Max	-40, 55	-35, 25

Higher scores indicate higher quality of life (range = 0 to 100). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

Alnylam Pharmaceuticals Inc.
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Table 7.5
EuroQol-Visual Analog Scale (EQ-VAS) Score: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Genotype: non-V30M

Subgroup Visit	Vutrisiran (HELIOS-A) (N=68)	Patisiran (HELIOS-A) (N=22)
Month 18		
Actual Value		
n	62	17
Mean (SD)	67.3 (19.4)	64.1 (16.7)
SE	2.5	4.1
Median	70.0	60.0
Min, Max	25, 100	35, 100
Change from baseline		
n	61	17
Mean (SD)	2.4 (19.9)	-4.5 (16.2)
SE	2.6	3.9
Median	2.0	0.0
Min, Max	-50, 50	-40, 15

Higher scores indicate higher quality of life (range = 0 to 100). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

Alnylam Pharmaceuticals Inc.
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Table 7.5
EuroQol-Visual Analog Scale (EQ-VAS) Score: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

FAP Stage: I

Subgroup Visit	Vutrisiran (HELIOS-A) (N=84)	Patisiran (HELIOS-A) (N=31)
Baseline		
n	83	30
Mean (SD)	69.0 (17.2)	67.7 (13.2)
SE	1.9	2.4
Median	70.0	70.0
Min, Max	25, 99	40, 90
Month 9		
Actual Value		
n	82	29
Mean (SD)	72.9 (15.5)	66.4 (15.9)
SE	1.7	2.9
Median	70.0	70.0
Min, Max	30, 100	30, 90
Change from baseline		
n	81	28
Mean (SD)	3.8 (14.6)	-2.0 (14.2)
SE	1.6	2.7
Median	0.0	-2.5
Min, Max	-32, 50	-35, 25

Higher scores indicate higher quality of life (range = 0 to 100). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

Alnylam Pharmaceuticals Inc.
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Table 7.5
EuroQol-Visual Analog Scale (EQ-VAS) Score: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

FAP Stage: I

Subgroup Visit	Vutrisiran (HELIOS-A) (N=84)	Patisiran (HELIOS-A) (N=31)
Month 18		
Actual Value		
n	81	29
Mean (SD)	71.1 (16.5)	65.0 (15.6)
SE	1.8	2.9
Median	70.0	65.0
Min, Max	30, 100	30, 100
Change from baseline		
n	80	29
Mean (SD)	1.6 (16.2)	-3.2 (15.0)
SE	1.8	2.8
Median	0.0	0.0
Min, Max	-40, 50	-40, 20

Higher scores indicate higher quality of life (range = 0 to 100). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

Alnylam Pharmaceuticals Inc.
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Table 7.5
EuroQol-Visual Analog Scale (EQ-VAS) Score: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

FAP Stage: II&III

Subgroup Visit	Vutrisiran (HELIOS-A) (N=38)	Patisiran (HELIOS-A) (N=11)
Baseline		
n	37	11
Mean (SD)	54.5 (17.5)	50.5 (17.2)
SE	2.9	5.2
Median	50.0	50.0
Min, Max	15, 90	20, 75
Month 9		
Actual Value		
n	33	10
Mean (SD)	55.2 (19.4)	51.0 (19.1)
SE	3.4	6.0
Median	55.0	52.5
Min, Max	5, 90	25, 80
Change from baseline		
n	33	10
Mean (SD)	-1.1 (22.7)	0.0 (13.1)
SE	3.9	4.1
Median	0.0	2.5
Min, Max	-60, 55	-25, 20

Higher scores indicate higher quality of life (range = 0 to 100). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

Alnylam Pharmaceuticals Inc.
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Table 7.5
EuroQol-Visual Analog Scale (EQ-VAS) Score: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

FAP Stage: II&III

Subgroup Visit	Vutrisiran (HELIOS-A) (N=38)	Patisiran (HELIOS-A) (N=11)
Month 18		
Actual Value		
n	33	8
Mean (SD)	58.5 (19.2)	56.3 (12.7)
SE	3.3	4.5
Median	60.0	57.5
Min, Max	25, 90	40, 75
Change from baseline		
n	32	8
Mean (SD)	2.3 (20.4)	0.0 (17.7)
SE	3.6	6.3
Median	2.5	2.5
Min, Max	-50, 40	-25, 25

Higher scores indicate higher quality of life (range = 0 to 100). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

Alnylam Pharmaceuticals Inc.
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Table 7.5
EuroQol-Visual Analog Scale (EQ-VAS) Score: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Cardiac Subpopulation: Yes

Subgroup Visit	Vutrisiran (HELIOS-A) (N=40)	Patisiran (HELIOS-A) (N=14)
Baseline		
n	39	14
Mean (SD)	62.2 (20.1)	58.9 (20.1)
SE	3.2	5.4
Median	65.0	60.0
Min, Max	25, 95	20, 90
Month 9		
Actual Value		
n	37	14
Mean (SD)	65.1 (17.6)	54.6 (21.9)
SE	2.9	5.8
Median	65.0	60.0
Min, Max	30, 100	25, 85
Change from baseline		
n	37	14
Mean (SD)	2.0 (16.1)	-4.3 (14.3)
SE	2.7	3.8
Median	0.0	-7.5
Min, Max	-40, 35	-25, 25

Higher scores indicate higher quality of life (range = 0 to 100). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

Alnylam Pharmaceuticals Inc.
ALN-TTRSC02-002

Table 7.5
EuroQol-Visual Analog Scale (EQ-VAS) Score: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Cardiac Subpopulation: Yes

Subgroup Visit	Vutrisiran (HELIOS-A) (N=40)	Patisiran (HELIOS-A) (N=14)
Month 18		
Actual Value		
n	37	13
Mean (SD)	62.5 (17.9)	60.3 (12.7)
SE	2.9	3.5
Median	60.0	60.0
Min, Max	25, 95	40, 79
Change from baseline		
n	36	13
Mean (SD)	-0.9 (19.9)	-1.6 (16.8)
SE	3.3	4.7
Median	0.0	0.0
Min, Max	-50, 40	-30, 25

Higher scores indicate higher quality of life (range = 0 to 100). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

Alnylam Pharmaceuticals Inc.
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Table 7.5
EuroQol-Visual Analog Scale (EQ-VAS) Score: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Cardiac Subpopulation: No

Subgroup Visit	Vutrisiran (HELIOS-A) (N=82)	Patisiran (HELIOS-A) (N=28)
Baseline		
n	81	27
Mean (SD)	65.6 (17.7)	65.2 (13.6)
SE	2.0	2.6
Median	65.0	70.0
Min, Max	15, 99	40, 90
Month 9		
Actual Value		
n	78	25
Mean (SD)	69.1 (18.9)	66.8 (13.8)
SE	2.1	2.8
Median	70.0	70.0
Min, Max	5, 100	40, 90
Change from baseline		
n	77	24
Mean (SD)	2.6 (18.0)	0.2 (13.6)
SE	2.1	2.8
Median	0.0	0.0
Min, Max	-60, 55	-35, 20

Higher scores indicate higher quality of life (range = 0 to 100). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

Alnylam Pharmaceuticals Inc.
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Table 7.5
EuroQol-Visual Analog Scale (EQ-VAS) Score: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Cardiac Subpopulation: No

Subgroup Visit	Vutrisiran (HELIOS-A) (N=82)	Patisiran (HELIOS-A) (N=28)
Month 18		
Actual Value		
n	77	24
Mean (SD)	69.9 (17.9)	64.7 (16.6)
SE	2.0	3.4
Median	70.0	65.0
Min, Max	30, 100	30, 100
Change from baseline		
n	76	24
Mean (SD)	3.1 (16.1)	-3.0 (15.0)
SE	1.8	3.1
Median	0.5	0.0
Min, Max	-35, 50	-40, 20

Higher scores indicate higher quality of life (range = 0 to 100). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

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Table 7.5
EuroQol-Visual Analog Scale (EQ-VAS) Score: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Weight (kg): <65

Subgroup Visit	Vutrisiran (HELIOS-A) (N=46)	Patisiran (HELIOS-A) (N=15)
Baseline		
n	46	14
Mean (SD)	65.4 (18.9)	65.0 (12.1)
SE	2.8	3.2
Median	66.5	70.0
Min, Max	25, 95	45, 80
Month 9		
Actual Value		
n	44	14
Mean (SD)	66.2 (16.9)	61.8 (19.3)
SE	2.5	5.2
Median	66.0	67.5
Min, Max	25, 100	25, 90
Change from baseline		
n	44	13
Mean (SD)	-0.1 (14.9)	-3.5 (18.5)
SE	2.2	5.1
Median	0.0	-5.0
Min, Max	-40, 35	-35, 20

Higher scores indicate higher quality of life (range = 0 to 100). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

Alnylam Pharmaceuticals Inc.
ALN-TTRSC02-002

Table 7.5
EuroQol-Visual Analog Scale (EQ-VAS) Score: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Weight (kg): <65

Subgroup Visit	Vutrisiran (HELIOS-A) (N=46)	Patisiran (HELIOS-A) (N=15)
Month 18		
Actual Value		
n	42	14
Mean (SD)	67.3 (18.5)	58.7 (15.3)
SE	2.8	4.1
Median	70.0	60.0
Min, Max	30, 95	30, 82
Change from baseline		
n	42	14
Mean (SD)	0.2 (19.5)	-6.3 (19.1)
SE	3.0	5.1
Median	0.0	-7.5
Min, Max	-50, 40	-40, 25

Higher scores indicate higher quality of life (range = 0 to 100). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

Alnylam Pharmaceuticals Inc.
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Table 7.5
EuroQol-Visual Analog Scale (EQ-VAS) Score: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Weight (kg): ≥65

Subgroup Visit	Vutrisiran (HELIOS-A) (N=76)	Patisiran (HELIOS-A) (N=27)
Baseline		
n	74	27
Mean (SD)	64.0 (18.4)	62.0 (18.0)
SE	2.1	3.5
Median	65.0	65.0
Min, Max	15, 99	20, 90
Month 9		
Actual Value		
n	71	25
Mean (SD)	68.8 (19.5)	62.8 (17.4)
SE	2.3	3.5
Median	70.0	65.0
Min, Max	5, 100	25, 90
Change from baseline		
n	70	25
Mean (SD)	4.0 (18.6)	-0.4 (10.9)
SE	2.2	2.2
Median	0.0	0.0
Min, Max	-60, 55	-20, 25

Higher scores indicate higher quality of life (range = 0 to 100). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

Alnylam Pharmaceuticals Inc.
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Table 7.5
EuroQol-Visual Analog Scale (EQ-VAS) Score: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Weight (kg): ≥65

Subgroup Visit	Vutrisiran (HELIOS-A) (N=76)	Patisiran (HELIOS-A) (N=27)
Month 18		
Actual Value		
n	72	23
Mean (SD)	67.6 (18.1)	65.8 (14.9)
SE	2.1	3.1
Median	70.0	65.0
Min, Max	25, 100	40, 100
Change from baseline		
n	70	23
Mean (SD)	2.7 (16.1)	-0.3 (12.7)
SE	1.9	2.6
Median	0.5	0.0
Min, Max	-35, 50	-30, 20

Higher scores indicate higher quality of life (range = 0 to 100). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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EQ-5D-VAS (Binäre Analyse)

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ALN-TTRSC02-002

Table 7.4
EuroQol-Visual Analog Scale (EQ-VAS) Score
Binary Subgroup Analysis
mITT Population

Month 9

Analysis Visit Statistics	Vutrisiran (HELIOS-A) (N=122)	Patisiran (HELIOS-A) (N=42)
Age (years)		
<65		
Patients included in analysis, N1	76	31
≥15 point increase from baseline, n(%)	15 (19.7)	5 (16.1)
<15 point increase from baseline, n(%)	58 (76.3)	23 (74.2)
Missing, n(%)	3 (3.9)	3 (9.7)
≥15 point increase from baseline, (95% CI)	19.7 (10.8, 28.7)	16.1 (3.2, 29.1)
Percentage difference (Vutrisiran − Patisiran), (95% CI)	3.608 (-12.131, 19.346)	
Odds ratio (Vutrisiran/Patisiran), (95% CI) [1]	1.279 (0.421, 3.885)	
Relative risk (Vutrisiran/Patisiran), (95% CI) [1]	1.224 (0.487, 3.076)	
P-value [2]	0.6678	

Higher scores indicate higher quality of life (range = 0 to 100). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.
[1] Based on unstratified analysis.
In estimation of the odds ratio and relative risk, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the percentage difference or p-value.
[2] p-value based on the Wald test testing whether the relative risk equals to 1.
[3] p-value from a logistic regression using the penalized likelihood estimation (the FIRTH option) and with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Alnylam Pharmaceuticals Inc.
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Table 7.4
EuroQol-Visual Analog Scale (EQ-VAS) Score
Binary Subgroup Analysis
mITT Population

Month 9

Analysis Visit Statistics	Vutrisiran (HELIOS-A) (N=122)	Patisiran (HELIOS-A) (N=42)
≥65		
Patients included in analysis, N1	46	11
≥15 point increase from baseline, n(%)	11 (23.9)	2 (18.2)
<15 point increase from baseline, n(%)	30 (65.2)	8 (72.7)
Missing, n(%)	5 (10.9)	1 (9.1)
≥15 point increase from baseline, (95% CI)	23.9 (11.6, 36.2)	18.2 (0.0, 41.0)
Percentage difference (Vutrisiran – Patisiran), (95% CI)	5.731 (-20.181, 31.644)	
Odds ratio (Vutrisiran/Patisiran), (95% CI) [1]	1.414 (0.265, 7.553)	
Relative risk (Vutrisiran/Patisiran), (95% CI) [1]	1.315 (0.339, 5.101)	
P-value [2]	0.6920	
p-value of Treatment*Age [3]	0.9890	

Higher scores indicate higher quality of life (range = 0 to 100). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.
[1] Based on unstratified analysis.
In estimation of the odds ratio and relative risk, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the percentage difference or p-value.
[2] p-value based on the Wald test testing whether the relative risk equals to 1.
[3] p-value from a logistic regression using the penalized likelihood estimation (the FIRTH option) and with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Alnylam Pharmaceuticals Inc.
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Table 7.4
EuroQol-Visual Analog Scale (EQ-VAS) Score
Binary Subgroup Analysis
mITT Population

Month 18

Analysis Visit Statistics	Vutrisiran (HELIOS-A) (N=122)	Patisiran (HELIOS-A) (N=42)
Age (years)		
<65		
Patients included in analysis, N1	76	31
≥15 point increase from baseline, n(%)	15 (19.7)	2 (6.5)
<15 point increase from baseline, n(%)	58 (76.3)	26 (83.9)
Missing, n(%)	3 (3.9)	3 (9.7)
≥15 point increase from baseline, (95% CI)	19.7 (10.8, 28.7)	6.5 (0.0, 15.1)
Percentage difference (Vutrisiran – Patisiran), (95% CI)	13.285 (0.841, 25.730)	
Odds ratio (Vutrisiran/Patisiran), (95% CI) [1]	3.566 (0.764, 16.636)	
Relative risk (Vutrisiran/Patisiran), (95% CI) [1]	3.059 (0.743, 12.594)	
P-value [2]	0.1214	

Higher scores indicate higher quality of life (range = 0 to 100). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.
[1] Based on unstratified analysis.
In estimation of the odds ratio and relative risk, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the percentage difference or p-value.
[2] p-value based on the Wald test testing whether the relative risk equals to 1.
[3] p-value from a logistic regression using the penalized likelihood estimation (the FIRTH option) and with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Table 7.4
EuroQol-Visual Analog Scale (EQ-VAS) Score
Binary Subgroup Analysis
mITT Population

Month 18

Analysis Visit Statistics	Vutrisiran (HELIOS-A) (N=122)	Patisiran (HELIOS-A) (N=42)
≥65		
Patients included in analysis, N1	46	11
≥15 point increase from baseline, n(%)	12 (26.1)	2 (18.2)
<15 point increase from baseline, n(%)	27 (58.7)	7 (63.6)
Missing, n(%)	7 (15.2)	2 (18.2)
≥15 point increase from baseline, (95% CI)	26.1 (13.4, 38.8)	18.2 (0.0, 41.0)
Percentage difference (Vutrisiran - Patisiran), (95% CI)	7.905 (-18.182, 33.992)	
Odds ratio (Vutrisiran/Patisiran), (95% CI) [1]	1.588 (0.300, 8.416)	
Relative risk (Vutrisiran/Patisiran), (95% CI) [1]	1.435 (0.374, 5.505)	
P-value [2]	0.5987	
p-value of Treatment*Age [3]	0.4803	

Higher scores indicate higher quality of life (range = 0 to 100). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.
[1] Based on unstratified analysis.
In estimation of the odds ratio and relative risk, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the percentage difference or p-value.
[2] p-value based on the Wald test testing whether the relative risk equals to 1.
[3] p-value from a logistic regression using the penalized likelihood estimation (the FIRTH option) and with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Alnylam Pharmaceuticals Inc.
ALN-TTRSC02-002

Table 7.4
EuroQol-Visual Analog Scale (EQ-VAS) Score
Binary Subgroup Analysis
mITT Population

Month 9

Analysis Visit Statistics	Vutrisiran (HELIOS-A) (N=122)	Patisiran (HELIOS-A) (N=42)
Sex		
Male		
Patients included in analysis, N1	79	27
≥15 point increase from baseline, n(%)	16 (20.3)	4 (14.8)
<15 point increase from baseline, n(%)	59 (74.7)	21 (77.8)
Missing, n(%)	4 (5.1)	2 (7.4)
≥15 point increase from baseline, (95% CI)	20.3 (11.4, 29.1)	14.8 (1.4, 28.2)
Percentage difference (Vutrisiran – Patisiran), (95% CI)	5.438 (-10.627, 21.504)	
Odds ratio (Vutrisiran/Patisiran), (95% CI) [1]	1.460 (0.442, 4.825)	
Relative risk (Vutrisiran/Patisiran), (95% CI) [1]	1.367 (0.501, 3.734)	
P-value [2]	0.5419	

Higher scores indicate higher quality of life (range = 0 to 100). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.
[1] Based on unstratified analysis.
In estimation of the odds ratio and relative risk, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the percentage difference or p-value.
[2] p-value based on the Wald test testing whether the relative risk equals to 1.
[3] p-value from a logistic regression using the penalized likelihood estimation (the FIRTH option) and with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Alnylam Pharmaceuticals Inc.
ALN-TTRSC02-002

Table 7.4
EuroQol-Visual Analog Scale (EQ-VAS) Score
Binary Subgroup Analysis
mITT Population

Month 9

Analysis Visit Statistics	Vutrisiran (HELIOS-A) (N=122)	Patisiran (HELIOS-A) (N=42)
Female		
Patients included in analysis, N1	43	15
≥15 point increase from baseline, n(%)	10 (23.3)	3 (20.0)
<15 point increase from baseline, n(%)	29 (67.4)	10 (66.7)
Missing, n(%)	4 (9.3)	2 (13.3)
≥15 point increase from baseline, (95% CI)	23.3 (10.6, 35.9)	20.0 (0.0, 40.2)
Percentage difference (Vutrisiran - Patisiran), (95% CI)	3.256 (-20.602, 27.114)	
Odds ratio (Vutrisiran/Patisiran), (95% CI) [1]	1.212 (0.284, 5.165)	
Relative risk (Vutrisiran/Patisiran), (95% CI) [1]	1.163 (0.369, 3.667)	
P-value [2]	0.7969	
p-value of Treatment*Sex [3]	0.8365	

Higher scores indicate higher quality of life (range = 0 to 100). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.
[1] Based on unstratified analysis.
In estimation of the odds ratio and relative risk, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the percentage difference or p-value.
[2] p-value based on the Wald test testing whether the relative risk equals to 1.
[3] p-value from a logistic regression using the penalized likelihood estimation (the FIRTH option) and with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Alnylam Pharmaceuticals Inc.
ALN-TTRSC02-002

Table 7.4
EuroQol-Visual Analog Scale (EQ-VAS) Score
Binary Subgroup Analysis
mITT Population

Month 18

Analysis Visit Statistics	Vutrisiran (HELIOS-A) (N=122)	Patisiran (HELIOS-A) (N=42)
Sex		
Male		
Patients included in analysis, N1	79	27
≥15 point increase from baseline, n(%)	18 (22.8)	2 (7.4)
<15 point increase from baseline, n(%)	55 (69.6)	21 (77.8)
Missing, n(%)	6 (7.6)	4 (14.8)
≥15 point increase from baseline, (95% CI)	22.8 (13.5, 32.0)	7.4 (0.0, 17.3)
Percentage difference (Vutrisiran – Patisiran), (95% CI)	15.377 (1.845, 28.910)	
Odds ratio (Vutrisiran/Patisiran), (95% CI) [1]	3.689 (0.796, 17.089)	
Relative risk (Vutrisiran/Patisiran), (95% CI) [1]	3.076 (0.763, 12.399)	
P-value [2]	0.1142	

Higher scores indicate higher quality of life (range = 0 to 100). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.
[1] Based on unstratified analysis.
In estimation of the odds ratio and relative risk, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the percentage difference or p-value.
[2] p-value based on the Wald test testing whether the relative risk equals to 1.
[3] p-value from a logistic regression using the penalized likelihood estimation (the FIRTH option) and with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Alnylam Pharmaceuticals Inc.
ALN-TTRSC02-002

Table 7.4
EuroQol-Visual Analog Scale (EQ-VAS) Score
Binary Subgroup Analysis
mITT Population

Month 18

Analysis Visit Statistics	Vutrisiran (HELIOS-A) (N=122)	Patisiran (HELIOS-A) (N=42)
Female		
Patients included in analysis, N1	43	15
≥15 point increase from baseline, n(%)	9 (20.9)	2 (13.3)
<15 point increase from baseline, n(%)	30 (69.8)	12 (80.0)
Missing, n(%)	4 (9.3)	1 (6.7)
≥15 point increase from baseline, (95% CI)	20.9 (8.8, 33.1)	13.3 (0.0, 30.5)
Percentage difference (Vutrisiran - Patisiran), (95% CI)	7.597 (-13.469, 28.663)	
Odds ratio (Vutrisiran/Patisiran), (95% CI) [1]	1.721 (0.327, 9.050)	
Relative risk (Vutrisiran/Patisiran), (95% CI) [1]	1.570 (0.381, 6.462)	
P-value [2]	0.5322	
p-value of Treatment*Sex [3]	0.5028	

Higher scores indicate higher quality of life (range = 0 to 100). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.
[1] Based on unstratified analysis.
In estimation of the odds ratio and relative risk, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the percentage difference or p-value.
[2] p-value based on the Wald test testing whether the relative risk equals to 1.
[3] p-value from a logistic regression using the penalized likelihood estimation (the FIRTH option) and with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Table 7.4
EuroQol-Visual Analog Scale (EQ-VAS) Score
Binary Subgroup Analysis
mITT Population

Month 9

Analysis Visit Statistics	Vutrisiran (HELIOS-A) (N=122)	Patisiran (HELIOS-A) (N=42)
Race		
White		
Patients included in analysis, N1	86	29
≥15 point increase from baseline, n(%)	13 (15.1)	3 (10.3)
<15 point increase from baseline, n(%)	67 (77.9)	23 (79.3)
Missing, n(%)	6 (7.0)	3 (10.3)
≥15 point increase from baseline, (95% CI)	15.1 (7.5, 22.7)	10.3 (0.0, 21.4)
Percentage difference (Vutrisiran – Patisiran), (95% CI)	4.771 (-8.651, 18.194)	
Odds ratio (Vutrisiran/Patisiran), (95% CI) [1]	1.543 (0.407, 5.852)	
Relative risk (Vutrisiran/Patisiran), (95% CI) [1]	1.461 (0.448, 4.768)	
P-value [2]	0.5297	

Higher scores indicate higher quality of life (range = 0 to 100). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.
[1] Based on unstratified analysis.
In estimation of the odds ratio and relative risk, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the percentage difference or p-value.
[2] p-value based on the Wald test testing whether the relative risk equals to 1.
[3] p-value from a logistic regression using the penalized likelihood estimation (the FIRTH option) and with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Table 7.4
EuroQol-Visual Analog Scale (EQ-VAS) Score
Binary Subgroup Analysis
mITT Population

Month 9

Analysis Visit Statistics	Vutrisiran (HELIOS-A) (N=122)	Patisiran (HELIOS-A) (N=42)
All Other Races		
Patients included in analysis, N1	36	13
≥15 point increase from baseline, n(%)	13 (36.1)	4 (30.8)
<15 point increase from baseline, n(%)	21 (58.3)	8 (61.5)
Missing, n(%)	2 (5.6)	1 (7.7)
≥15 point increase from baseline, (95% CI)	36.1 (20.4, 51.8)	30.8 (5.7, 55.9)
Percentage difference (Vutrisiran - Patisiran), (95% CI)	5.342 (-24.249, 34.933)	
Odds ratio (Vutrisiran/Patisiran), (95% CI) [1]	1.272 (0.326, 4.955)	
Relative risk (Vutrisiran/Patisiran), (95% CI) [1]	1.174 (0.466, 2.957)	
P-value [2]	0.7342	
p-value of Treatment*Race [3]	0.8851	

Higher scores indicate higher quality of life (range = 0 to 100). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.
[1] Based on unstratified analysis.
In estimation of the odds ratio and relative risk, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the percentage difference or p-value.
[2] p-value based on the Wald test testing whether the relative risk equals to 1.
[3] p-value from a logistic regression using the penalized likelihood estimation (the FIRTH option) and with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Table 7.4
EuroQol-Visual Analog Scale (EQ-VAS) Score
Binary Subgroup Analysis
mITT Population

Month 18

Analysis Visit Statistics	Vutrisiran (HELIOS-A) (N=122)	Patisiran (HELIOS-A) (N=42)
Race		
White		
Patients included in analysis, N1	86	29
≥15 point increase from baseline, n(%)	17 (19.8)	3 (10.3)
<15 point increase from baseline, n(%)	62 (72.1)	23 (79.3)
Missing, n(%)	7 (8.1)	3 (10.3)
≥15 point increase from baseline, (95% CI)	19.8 (11.4, 28.2)	10.3 (0.0, 21.4)
Percentage difference (Vutrisiran – Patisiran), (95% CI)	9.423 (-4.495, 23.340)	
Odds ratio (Vutrisiran/Patisiran), (95% CI) [1]	2.135 (0.578, 7.895)	
Relative risk (Vutrisiran/Patisiran), (95% CI) [1]	1.911 (0.603, 6.053)	
P-value [2]	0.2710	

Higher scores indicate higher quality of life (range = 0 to 100). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.
[1] Based on unstratified analysis.
In estimation of the odds ratio and relative risk, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the percentage difference or p-value.
[2] p-value based on the Wald test testing whether the relative risk equals to 1.
[3] p-value from a logistic regression using the penalized likelihood estimation (the FIRTH option) and with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Table 7.4
EuroQol-Visual Analog Scale (EQ-VAS) Score
Binary Subgroup Analysis
mITT Population

Month 18

Analysis Visit Statistics	Vutrisiran (HELIOS-A) (N=122)	Patisiran (HELIOS-A) (N=42)
All Other Races		
Patients included in analysis, N1	36	13
≥15 point increase from baseline, n(%)	10 (27.8)	1 (7.7)
<15 point increase from baseline, n(%)	23 (63.9)	10 (76.9)
Missing, n(%)	3 (8.3)	2 (15.4)
≥15 point increase from baseline, (95% CI)	27.8 (13.1, 42.4)	7.7 (0.0, 22.2)
Percentage difference (Vutrisiran - Patisiran), (95% CI)	20.085 (-0.503, 40.674)	
Odds ratio (Vutrisiran/Patisiran), (95% CI) [1]	4.615 (0.529, 40.279)	
Relative risk (Vutrisiran/Patisiran), (95% CI) [1]	3.611 (0.511, 25.518)	
P-value [2]	0.1981	
p-value of Treatment*Race [3]	0.6363	

Higher scores indicate higher quality of life (range = 0 to 100). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.
[1] Based on unstratified analysis.
In estimation of the odds ratio and relative risk, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the percentage difference or p-value.
[2] p-value based on the Wald test testing whether the relative risk equals to 1.
[3] p-value from a logistic regression using the penalized likelihood estimation (the FIRTH option) and with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Table 7.4
EuroQol-Visual Analog Scale (EQ-VAS) Score
Binary Subgroup Analysis
mITT Population

Month 9

Analysis Visit Statistics	Vutrisiran (HELIOS-A) (N=122)	Patisiran (HELIOS-A) (N=42)
Region		
North America		
Patients included in analysis, N1	27	8
≥15 point increase from baseline, n(%)	9 (33.3)	1 (12.5)
<15 point increase from baseline, n(%)	15 (55.6)	7 (87.5)
Missing, n(%)	3 (11.1)	0
≥15 point increase from baseline, (95% CI)	33.3 (15.6, 51.1)	12.5 (0.0, 35.4)
Percentage difference (Vutrisiran – Patisiran), (95% CI)	20.833 (-8.173, 49.840)	
Odds ratio (Vutrisiran/Patisiran), (95% CI) [1]	3.500 (0.372, 32.971)	
Relative risk (Vutrisiran/Patisiran), (95% CI) [1]	2.667 (0.395, 17.998)	
P-value [2]	0.3140	

Higher scores indicate higher quality of life (range = 0 to 100). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.
[1] Based on unstratified analysis.
In estimation of the odds ratio and relative risk, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the percentage difference or p-value.
[2] p-value based on the Wald test testing whether the relative risk equals to 1.
[3] p-value from a logistic regression using the penalized likelihood estimation (the FIRTH option) and with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Table 7.4
EuroQol-Visual Analog Scale (EQ-VAS) Score
Binary Subgroup Analysis
mITT Population

Month 9

Analysis Visit Statistics	Vutrisiran (HELIOS-A) (N=122)	Patisiran (HELIOS-A) (N=42)
Western Europe		
Patients included in analysis, N1	42	20
≥15 point increase from baseline, n(%)	3 (7.1)	4 (20.0)
<15 point increase from baseline, n(%)	35 (83.3)	13 (65.0)
Missing, n(%)	4 (9.5)	3 (15.0)
≥15 point increase from baseline, (95% CI)	7.1 (0.0, 14.9)	20.0 (2.5, 37.5)
Percentage difference (Vutrisiran – Patisiran), (95% CI)	-12.857 (-32.040, 6.326)	
Odds ratio (Vutrisiran/Patisiran), (95% CI) [1]	0.308 (0.062, 1.533)	
Relative risk (Vutrisiran/Patisiran), (95% CI) [1]	0.357 (0.088, 1.447)	
P-value [2]	0.1492	

Higher scores indicate higher quality of life (range = 0 to 100). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.
[1] Based on unstratified analysis.
In estimation of the odds ratio and relative risk, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the percentage difference or p-value.
[2] p-value based on the Wald test testing whether the relative risk equals to 1.
[3] p-value from a logistic regression using the penalized likelihood estimation (the FIRTH option) and with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Table 7.4
EuroQol-Visual Analog Scale (EQ-VAS) Score
Binary Subgroup Analysis
mITT Population

Month 9

Analysis Visit Statistics	Vutrisiran (HELIOS-A) (N=122)	Patisiran (HELIOS-A) (N=42)
Rest of World		
Patients included in analysis, N1	53	14
≥15 point increase from baseline, n(%)	14 (26.4)	2 (14.3)
<15 point increase from baseline, n(%)	38 (71.7)	11 (78.6)
Missing, n(%)	1 (1.9)	1 (7.1)
≥15 point increase from baseline, (95% CI)	26.4 (14.5, 38.3)	14.3 (0.0, 32.6)
Percentage difference (Vutrisiran - Patisiran), (95% CI)	12.129 (-9.708, 33.967)	
Odds ratio (Vutrisiran/Patisiran), (95% CI) [1]	2.154 (0.428, 10.848)	
Relative risk (Vutrisiran/Patisiran), (95% CI) [1]	1.849 (0.475, 7.201)	
P-value [2]	0.3755	
p-value of Treatment*Region [3]	0.1743	

Higher scores indicate higher quality of life (range = 0 to 100). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.
[1] Based on unstratified analysis.
In estimation of the odds ratio and relative risk, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the percentage difference or p-value.
[2] p-value based on the Wald test testing whether the relative risk equals to 1.
[3] p-value from a logistic regression using the penalized likelihood estimation (the FIRTH option) and with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Table 7.4
EuroQol-Visual Analog Scale (EQ-VAS) Score
Binary Subgroup Analysis
mITT Population

Month 18

Analysis Visit Statistics	Vutrisiran (HELIOS-A) (N=122)	Patisiran (HELIOS-A) (N=42)
Region		
North America		
Patients included in analysis, N1	27	8
≥15 point increase from baseline, n(%)	8 (29.6)	0
<15 point increase from baseline, n(%)	16 (59.3)	7 (87.5)
Missing, n(%)	3 (11.1)	1 (12.5)
≥15 point increase from baseline, (95% CI)	29.6 (12.4, 46.9)	0.0 (0.0, 0.0)
Percentage difference (Vutrisiran – Patisiran), (95% CI)	29.630 (12.406, 46.853)	
Odds ratio (Vutrisiran/Patisiran), (95% CI) [1]	7.410 (0.383, 143.540)	
Relative risk (Vutrisiran/Patisiran), (95% CI) [1]	5.464 (0.349, 85.605)	
P-value [2]	0.2264	

Higher scores indicate higher quality of life (range = 0 to 100). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.
[1] Based on unstratified analysis.
In estimation of the odds ratio and relative risk, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the percentage difference or p-value.
[2] p-value based on the Wald test testing whether the relative risk equals to 1.
[3] p-value from a logistic regression using the penalized likelihood estimation (the FIRTH option) and with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Table 7.4
EuroQol-Visual Analog Scale (EQ-VAS) Score
Binary Subgroup Analysis
mITT Population

Month 18

Analysis Visit Statistics	Vutrisiran (HELIOS-A) (N=122)	Patisiran (HELIOS-A) (N=42)
Western Europe		
Patients included in analysis, N1	42	20
≥15 point increase from baseline, n(%)	8 (19.0)	2 (10.0)
<15 point increase from baseline, n(%)	30 (71.4)	15 (75.0)
Missing, n(%)	4 (9.5)	3 (15.0)
≥15 point increase from baseline, (95% CI)	19.0 (7.2, 30.9)	10.0 (0.0, 23.1)
Percentage difference (Vutrisiran – Patisiran), (95% CI)	9.048 (-8.670, 26.765)	
Odds ratio (Vutrisiran/Patisiran), (95% CI) [1]	2.118 (0.406, 11.043)	
Relative risk (Vutrisiran/Patisiran), (95% CI) [1]	1.905 (0.445, 8.162)	
P-value [2]	0.3854	

Higher scores indicate higher quality of life (range = 0 to 100). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.
[1] Based on unstratified analysis.
In estimation of the odds ratio and relative risk, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the percentage difference or p-value.
[2] p-value based on the Wald test testing whether the relative risk equals to 1.
[3] p-value from a logistic regression using the penalized likelihood estimation (the FIRTH option) and with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Table 7.4
EuroQol-Visual Analog Scale (EQ-VAS) Score
Binary Subgroup Analysis
mITT Population

Month 18

Analysis Visit Statistics	Vutrisiran (HELIOS-A) (N=122)	Patisiran (HELIOS-A) (N=42)
Rest of World		
Patients included in analysis, N1	53	14
≥15 point increase from baseline, n(%)	11 (20.8)	2 (14.3)
<15 point increase from baseline, n(%)	39 (73.6)	11 (78.6)
Missing, n(%)	3 (5.7)	1 (7.1)
≥15 point increase from baseline, (95% CI)	20.8 (9.8, 31.7)	14.3 (0.0, 32.6)
Percentage difference (Vutrisiran - Patisiran), (95% CI)	6.469 (-14.866, 27.804)	
Odds ratio (Vutrisiran/Patisiran), (95% CI) [1]	1.571 (0.306, 8.081)	
Relative risk (Vutrisiran/Patisiran), (95% CI) [1]	1.453 (0.363, 5.814)	
P-value [2]	0.5976	
p-value of Treatment*Region [3]	0.6347	

Higher scores indicate higher quality of life (range = 0 to 100). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.
[1] Based on unstratified analysis.
In estimation of the odds ratio and relative risk, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the percentage difference or p-value.
[2] p-value based on the Wald test testing whether the relative risk equals to 1.
[3] p-value from a logistic regression using the penalized likelihood estimation (the FIRTH option) and with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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ALN-TTRSC02-002

Table 7.4
EuroQol-Visual Analog Scale (EQ-VAS) Score
Binary Subgroup Analysis
mITT Population

Month 9

Analysis Visit Statistics	Vutrisiran (HELIOS-A) (N=122)	Patisiran (HELIOS-A) (N=42)
Baseline NIS		
<50		
Patients included in analysis, N1	78	27
≥15 point increase from baseline, n(%)	20 (25.6)	6 (22.2)
<15 point increase from baseline, n(%)	56 (71.8)	19 (70.4)
Missing, n(%)	2 (2.6)	2 (7.4)
≥15 point increase from baseline, (95% CI)	25.6 (16.0, 35.3)	22.2 (6.5, 37.9)
Percentage difference (Vutrisiran – Patisiran), (95% CI)	3.419 (-15.015, 21.853)	
Odds ratio (Vutrisiran/Patisiran), (95% CI) [1]	1.207 (0.427, 3.414)	
Relative risk (Vutrisiran/Patisiran), (95% CI) [1]	1.154 (0.518, 2.569)	
P-value [2]	0.7261	

Higher scores indicate higher quality of life (range = 0 to 100). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.
[1] Based on unstratified analysis.
In estimation of the odds ratio and relative risk, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the percentage difference or p-value.
[2] p-value based on the Wald test testing whether the relative risk equals to 1.
[3] p-value from a logistic regression using the penalized likelihood estimation (the FIRTH option) and with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Alnylam Pharmaceuticals Inc.
ALN-TTRSC02-002

Table 7.4
EuroQol-Visual Analog Scale (EQ-VAS) Score
Binary Subgroup Analysis
mITT Population

Month 9

Analysis Visit Statistics	Vutrisiran (HELIOS-A) (N=122)	Patisiran (HELIOS-A) (N=42)
≥50		
Patients included in analysis, N1	44	15
≥15 point increase from baseline, n(%)	6 (13.6)	1 (6.7)
<15 point increase from baseline, n(%)	32 (72.7)	12 (80.0)
Missing, n(%)	6 (13.6)	2 (13.3)
≥15 point increase from baseline, (95% CI)	13.6 (3.5, 23.8)	6.7 (0.0, 19.3)
Percentage difference (Vutrisiran - Patisiran), (95% CI)	6.970 (-9.222, 23.161)	
Odds ratio (Vutrisiran/Patisiran), (95% CI) [1]	2.211 (0.244, 20.028)	
Relative risk (Vutrisiran/Patisiran), (95% CI) [1]	2.045 (0.267, 15.641)	
P-value [2]	0.4905	
p-value of Treatment*Baseline NIS [3]	0.7588	

Higher scores indicate higher quality of life (range = 0 to 100). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.
[1] Based on unstratified analysis.
In estimation of the odds ratio and relative risk, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the percentage difference or p-value.
[2] p-value based on the Wald test testing whether the relative risk equals to 1.
[3] p-value from a logistic regression using the penalized likelihood estimation (the FIRTH option) and with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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ALN-TTRSC02-002

Table 7.4
EuroQol-Visual Analog Scale (EQ-VAS) Score
Binary Subgroup Analysis
mITT Population

Month 18

Analysis Visit Statistics	Vutrisiran (HELIOS-A) (N=122)	Patisiran (HELIOS-A) (N=42)
Baseline NIS		
<50		
Patients included in analysis, N1	78	27
≥15 point increase from baseline, n(%)	20 (25.6)	1 (3.7)
<15 point increase from baseline, n(%)	54 (69.2)	24 (88.9)
Missing, n(%)	4 (5.1)	2 (7.4)
≥15 point increase from baseline, (95% CI)	25.6 (16.0, 35.3)	3.7 (0.0, 10.8)
Percentage difference (Vutrisiran – Patisiran), (95% CI)	21.937 (9.911, 33.964)	
Odds ratio (Vutrisiran/Patisiran), (95% CI) [1]	8.966 (1.142, 70.410)	
Relative risk (Vutrisiran/Patisiran), (95% CI) [1]	6.923 (0.975, 49.154)	
P-value [2]	0.0530	

Higher scores indicate higher quality of life (range = 0 to 100). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.
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In estimation of the odds ratio and relative risk, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the percentage difference or p-value.
[2] p-value based on the Wald test testing whether the relative risk equals to 1.
[3] p-value from a logistic regression using the penalized likelihood estimation (the FIRTH option) and with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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ALN-TTRSC02-002

Table 7.4
EuroQol-Visual Analog Scale (EQ-VAS) Score
Binary Subgroup Analysis
mITT Population

Month 18

Analysis Visit Statistics	Vutrisiran (HELIOS-A) (N=122)	Patisiran (HELIOS-A) (N=42)
≥50		
Patients included in analysis, N1	44	15
≥15 point increase from baseline, n(%)	7 (15.9)	3 (20.0)
<15 point increase from baseline, n(%)	31 (70.5)	9 (60.0)
Missing, n(%)	6 (13.6)	3 (20.0)
≥15 point increase from baseline, (95% CI)	15.9 (5.1, 26.7)	20.0 (0.0, 40.2)
Percentage difference (Vutrisiran – Patisiran), (95% CI)	-4.091 (-27.038, 18.856)	
Odds ratio (Vutrisiran/Patisiran), (95% CI) [1]	0.757 (0.169, 3.395)	
Relative risk (Vutrisiran/Patisiran), (95% CI) [1]	0.795 (0.235, 2.692)	
P-value [2]	0.7129	
p-value of Treatment*Baseline NIS [3]	0.0632	

Higher scores indicate higher quality of life (range = 0 to 100). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.
[1] Based on unstratified analysis.
In estimation of the odds ratio and relative risk, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the percentage difference or p-value.
[2] p-value based on the Wald test testing whether the relative risk equals to 1.
[3] p-value from a logistic regression using the penalized likelihood estimation (the FIRTH option) and with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Alnylam Pharmaceuticals Inc.
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Table 7.4
EuroQol-Visual Analog Scale (EQ-VAS) Score
Binary Subgroup Analysis
mITT Population

Month 9

Analysis Visit Statistics	Vutrisiran (HELIOS-A) (N=122)	Patisiran (HELIOS-A) (N=42)
Previous Tetramer Stabilizer Use		
Yes		
Patients included in analysis, N1	75	33
≥15 point increase from baseline, n(%)	14 (18.7)	6 (18.2)
<15 point increase from baseline, n(%)	59 (78.7)	25 (75.8)
Missing, n(%)	2 (2.7)	2 (6.1)
≥15 point increase from baseline, (95% CI)	18.7 (9.8, 27.5)	18.2 (5.0, 31.3)
Percentage difference (Vutrisiran – Patisiran), (95% CI)	0.485 (-15.356, 16.326)	
Odds ratio (Vutrisiran/Patisiran), (95% CI) [1]	1.033 (0.358, 2.976)	
Relative risk (Vutrisiran/Patisiran), (95% CI) [1]	1.027 (0.433, 2.437)	
P-value [2]	0.9524	

Higher scores indicate higher quality of life (range = 0 to 100). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.
[1] Based on unstratified analysis.
In estimation of the odds ratio and relative risk, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the percentage difference or p-value.
[2] p-value based on the Wald test testing whether the relative risk equals to 1.
[3] p-value from a logistic regression using the penalized likelihood estimation (the FIRTH option) and with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Table 7.4
EuroQol-Visual Analog Scale (EQ-VAS) Score
Binary Subgroup Analysis
mITT Population

Month 9

Analysis Visit Statistics	Vutrisiran (HELIOS-A) (N=122)	Patisiran (HELIOS-A) (N=42)
No		
Patients included in analysis, N1	47	9
≥15 point increase from baseline, n(%)	12 (25.5)	1 (11.1)
<15 point increase from baseline, n(%)	29 (61.7)	6 (66.7)
Missing, n(%)	6 (12.8)	2 (22.2)
≥15 point increase from baseline, (95% CI)	25.5 (13.1, 38.0)	11.1 (0.0, 31.6)
Percentage difference (Vutrisiran - Patisiran), (95% CI)	14.421 (-9.599, 38.441)	
Odds ratio (Vutrisiran/Patisiran), (95% CI) [1]	2.743 (0.310, 24.259)	
Relative risk (Vutrisiran/Patisiran), (95% CI) [1]	2.298 (0.340, 15.538)	
P-value [2]	0.3936	
p-value of Treatment*Previous Tetramer Stabilizer Use [3]	0.5375	

Higher scores indicate higher quality of life (range = 0 to 100). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.
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In estimation of the odds ratio and relative risk, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the percentage difference or p-value.
[2] p-value based on the Wald test testing whether the relative risk equals to 1.
[3] p-value from a logistic regression using the penalized likelihood estimation (the FIRTH option) and with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Table 7.4
EuroQol-Visual Analog Scale (EQ-VAS) Score
Binary Subgroup Analysis
mITT Population

Month 18

Analysis Visit Statistics	Vutrisiran (HELIOS-A) (N=122)	Patisiran (HELIOS-A) (N=42)
Previous Tetramer Stabilizer Use		
Yes		
Patients included in analysis, N1	75	33
≥15 point increase from baseline, n(%)	10 (13.3)	4 (12.1)
<15 point increase from baseline, n(%)	60 (80.0)	26 (78.8)
Missing, n(%)	5 (6.7)	3 (9.1)
≥15 point increase from baseline, (95% CI)	13.3 (5.6, 21.0)	12.1 (1.0, 23.3)
Percentage difference (Vutrisiran – Patisiran), (95% CI)	1.212 (-12.322, 14.747)	
Odds ratio (Vutrisiran/Patisiran), (95% CI) [1]	1.115 (0.323, 3.852)	
Relative risk (Vutrisiran/Patisiran), (95% CI) [1]	1.100 (0.372, 3.255)	
P-value [2]	0.8633	

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In estimation of the odds ratio and relative risk, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the percentage difference or p-value.
[2] p-value based on the Wald test testing whether the relative risk equals to 1.
[3] p-value from a logistic regression using the penalized likelihood estimation (the FIRTH option) and with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Alnylam Pharmaceuticals Inc.
ALN-TTRSC02-002

Table 7.4
EuroQol-Visual Analog Scale (EQ-VAS) Score
Binary Subgroup Analysis
mITT Population

Month 18

Analysis Visit Statistics	Vutrisiran (HELIOS-A) (N=122)	Patisiran (HELIOS-A) (N=42)
No		
Patients included in analysis, N1	47	9
≥15 point increase from baseline, n(%)	17 (36.2)	0
<15 point increase from baseline, n(%)	25 (53.2)	7 (77.8)
Missing, n(%)	5 (10.6)	2 (22.2)
≥15 point increase from baseline, (95% CI)	36.2 (22.4, 49.9)	0.0 (0.0, 0.0)
Percentage difference (Vutrisiran - Patisiran), (95% CI)	36.170 (22.433, 49.907)	
Odds ratio (Vutrisiran/Patisiran), (95% CI) [1]	10.902 (0.597, 198.906)	
Relative risk (Vutrisiran/Patisiran), (95% CI) [1]	7.292 (0.477, 111.503)	
P-value [2]	0.1534	
p-value of Treatment*Previous Tetramer Stabilizer Use [3]	0.1626	

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[1] Based on unstratified analysis.
In estimation of the odds ratio and relative risk, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the percentage difference or p-value.
[2] p-value based on the Wald test testing whether the relative risk equals to 1.
[3] p-value from a logistic regression using the penalized likelihood estimation (the FIRTH option) and with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Table 7.4
EuroQol-Visual Analog Scale (EQ-VAS) Score
Binary Subgroup Analysis
mITT Population

Month 9

Analysis Visit Statistics	Vutrisiran (HELIOS-A) (N=122)	Patisiran (HELIOS-A) (N=42)
Genotype		
V30M		
Patients included in analysis, N1	54	20
≥15 point increase from baseline, n(%)	5 (9.3)	5 (25.0)
<15 point increase from baseline, n(%)	46 (85.2)	14 (70.0)
Missing, n(%)	3 (5.6)	1 (5.0)
≥15 point increase from baseline, (95% CI)	9.3 (1.5, 17.0)	25.0 (6.0, 44.0)
Percentage difference (Vutrisiran – Patisiran), (95% CI)	-15.741 (-36.232, 4.751)	
Odds ratio (Vutrisiran/Patisiran), (95% CI) [1]	0.306 (0.078, 1.202)	
Relative risk (Vutrisiran/Patisiran), (95% CI) [1]	0.370 (0.120, 1.145)	
P-value [2]	0.0845	

Higher scores indicate higher quality of life (range = 0 to 100). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.
[1] Based on unstratified analysis.
In estimation of the odds ratio and relative risk, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the percentage difference or p-value.
[2] p-value based on the Wald test testing whether the relative risk equals to 1.
[3] p-value from a logistic regression using the penalized likelihood estimation (the FIRTH option) and with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Table 7.4
EuroQol-Visual Analog Scale (EQ-VAS) Score
Binary Subgroup Analysis
mITT Population

Month 9

Analysis Visit Statistics	Vutrisiran (HELIOS-A) (N=122)	Patisiran (HELIOS-A) (N=42)
non-V30M		
Patients included in analysis, N1	68	22
≥15 point increase from baseline, n(%)	21 (30.9)	2 (9.1)
<15 point increase from baseline, n(%)	42 (61.8)	17 (77.3)
Missing, n(%)	5 (7.4)	3 (13.6)
≥15 point increase from baseline, (95% CI)	30.9 (19.9, 41.9)	9.1 (0.0, 21.1)
Percentage difference (Vutrisiran - Patisiran), (95% CI)	21.791 (5.516, 38.067)	
Odds ratio (Vutrisiran/Patisiran), (95% CI) [1]	4.468 (0.956, 20.881)	
Relative risk (Vutrisiran/Patisiran), (95% CI) [1]	3.397 (0.865, 13.347)	
P-value [2]	0.0798	
p-value of Treatment*Genotype [3]	0.0135	

Higher scores indicate higher quality of life (range = 0 to 100). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.
[1] Based on unstratified analysis.
In estimation of the odds ratio and relative risk, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the percentage difference or p-value.
[2] p-value based on the Wald test testing whether the relative risk equals to 1.
[3] p-value from a logistic regression using the penalized likelihood estimation (the FIRTH option) and with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Table 7.4
EuroQol-Visual Analog Scale (EQ-VAS) Score
Binary Subgroup Analysis
mITT Population

Month 18

Analysis Visit Statistics	Vutrisiran (HELIOS-A) (N=122)	Patisiran (HELIOS-A) (N=42)
Genotype		
V30M		
Patients included in analysis, N1	54	20
≥15 point increase from baseline, n(%)	11 (20.4)	3 (15.0)
<15 point increase from baseline, n(%)	40 (74.1)	17 (85.0)
Missing, n(%)	3 (5.6)	0
≥15 point increase from baseline, (95% CI)	20.4 (9.6, 31.1)	15.0 (0.0, 30.6)
Percentage difference (Vutrisiran – Patisiran), (95% CI)	5.370 (-13.611, 24.352)	
Odds ratio (Vutrisiran/Patisiran), (95% CI) [1]	1.450 (0.359, 5.847)	
Relative risk (Vutrisiran/Patisiran), (95% CI) [1]	1.358 (0.422, 4.371)	
P-value [2]	0.6079	

Higher scores indicate higher quality of life (range = 0 to 100). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.
[1] Based on unstratified analysis.
In estimation of the odds ratio and relative risk, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the percentage difference or p-value.
[2] p-value based on the Wald test testing whether the relative risk equals to 1.
[3] p-value from a logistic regression using the penalized likelihood estimation (the FIRTH option) and with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Table 7.4
EuroQol-Visual Analog Scale (EQ-VAS) Score
Binary Subgroup Analysis
mITT Population

Month 18

Analysis Visit Statistics	Vutrisiran (HELIOS-A) (N=122)	Patisiran (HELIOS-A) (N=42)
non-V30M		
Patients included in analysis, N1	68	22
≥15 point increase from baseline, n(%)	16 (23.5)	1 (4.5)
<15 point increase from baseline, n(%)	45 (66.2)	16 (72.7)
Missing, n(%)	7 (10.3)	5 (22.7)
≥15 point increase from baseline, (95% CI)	23.5 (13.4, 33.6)	4.5 (0.0, 13.2)
Percentage difference (Vutrisiran - Patisiran), (95% CI)	18.984 (5.665, 32.303)	
Odds ratio (Vutrisiran/Patisiran), (95% CI) [1]	6.462 (0.805, 51.870)	
Relative risk (Vutrisiran/Patisiran), (95% CI) [1]	5.176 (0.728, 36.832)	
P-value [2]	0.1005	
p-value of Treatment*Genotype [3]	0.2819	

Higher scores indicate higher quality of life (range = 0 to 100). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.
[1] Based on unstratified analysis.
In estimation of the odds ratio and relative risk, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the percentage difference or p-value.
[2] p-value based on the Wald test testing whether the relative risk equals to 1.
[3] p-value from a logistic regression using the penalized likelihood estimation (the FIRTH option) and with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Table 7.4
EuroQol-Visual Analog Scale (EQ-VAS) Score
Binary Subgroup Analysis
mITT Population

Month 9

Analysis Visit Statistics	Vutrisiran (HELIOS-A) (N=122)	Patisiran (HELIOS-A) (N=42)
FAP Stage		
I		
Patients included in analysis, N1	84	31
≥15 point increase from baseline, n(%)	18 (21.4)	5 (16.1)
<15 point increase from baseline, n(%)	63 (75.0)	23 (74.2)
Missing, n(%)	3 (3.6)	3 (9.7)
≥15 point increase from baseline, (95% CI)	21.4 (12.7, 30.2)	16.1 (3.2, 29.1)
Percentage difference (Vutrisiran – Patisiran), (95% CI)	5.300 (-10.341, 20.940)	
Odds ratio (Vutrisiran/Patisiran), (95% CI) [1]	1.418 (0.477, 4.217)	
Relative risk (Vutrisiran/Patisiran), (95% CI) [1]	1.329 (0.540, 3.271)	
P-value [2]	0.5366	

Higher scores indicate higher quality of life (range = 0 to 100). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.
[1] Based on unstratified analysis.
In estimation of the odds ratio and relative risk, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the percentage difference or p-value.
[2] p-value based on the Wald test testing whether the relative risk equals to 1.
[3] p-value from a logistic regression using the penalized likelihood estimation (the FIRTH option) and with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Table 7.4
EuroQol-Visual Analog Scale (EQ-VAS) Score
Binary Subgroup Analysis
mITT Population

Month 9

Analysis Visit Statistics	Vutrisiran (HELIOS-A) (N=122)	Patisiran (HELIOS-A) (N=42)
II&III		
Patients included in analysis, N1	38	11
≥15 point increase from baseline, n(%)	8 (21.1)	2 (18.2)
<15 point increase from baseline, n(%)	25 (65.8)	8 (72.7)
Missing, n(%)	5 (13.2)	1 (9.1)
≥15 point increase from baseline, (95% CI)	21.1 (8.1, 34.0)	18.2 (0.0, 41.0)
Percentage difference (Vutrisiran - Patisiran), (95% CI)	2.871 (-23.350, 29.091)	
Odds ratio (Vutrisiran/Patisiran), (95% CI) [1]	1.200 (0.215, 6.696)	
Relative risk (Vutrisiran/Patisiran), (95% CI) [1]	1.158 (0.286, 4.680)	
P-value [2]	0.8370	
p-value of Treatment*FAP Stage [3]	0.8137	

Higher scores indicate higher quality of life (range = 0 to 100). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.
[1] Based on unstratified analysis.
In estimation of the odds ratio and relative risk, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the percentage difference or p-value.
[2] p-value based on the Wald test testing whether the relative risk equals to 1.
[3] p-value from a logistic regression using the penalized likelihood estimation (the FIRTH option) and with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Alnylam Pharmaceuticals Inc.
ALN-TTRSC02-002

Table 7.4
EuroQol-Visual Analog Scale (EQ-VAS) Score
Binary Subgroup Analysis
mITT Population

Month 18

Analysis Visit Statistics	Vutrisiran (HELIOS-A) (N=122)	Patisiran (HELIOS-A) (N=42)
FAP Stage		
I		
Patients included in analysis, N1	84	31
≥15 point increase from baseline, n(%)	16 (19.0)	2 (6.5)
<15 point increase from baseline, n(%)	64 (76.2)	27 (87.1)
Missing, n(%)	4 (4.8)	2 (6.5)
≥15 point increase from baseline, (95% CI)	19.0 (10.7, 27.4)	6.5 (0.0, 15.1)
Percentage difference (Vutrisiran – Patisiran), (95% CI)	12.596 (0.542, 24.650)	
Odds ratio (Vutrisiran/Patisiran), (95% CI) [1]	3.412 (0.737, 15.802)	
Relative risk (Vutrisiran/Patisiran), (95% CI) [1]	2.952 (0.720, 12.106)	
P-value [2]	0.1327	

Higher scores indicate higher quality of life (range = 0 to 100). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.
[1] Based on unstratified analysis.
In estimation of the odds ratio and relative risk, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the percentage difference or p-value.
[2] p-value based on the Wald test testing whether the relative risk equals to 1.
[3] p-value from a logistic regression using the penalized likelihood estimation (the FIRTH option) and with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Alnylam Pharmaceuticals Inc.
ALN-TTRSC02-002

Table 7.4
EuroQol-Visual Analog Scale (EQ-VAS) Score
Binary Subgroup Analysis
mITT Population

Month 18

Analysis Visit Statistics	Vutrisiran (HELIOS-A) (N=122)	Patisiran (HELIOS-A) (N=42)
II&III		
Patients included in analysis, N1	38	11
≥15 point increase from baseline, n(%)	11 (28.9)	2 (18.2)
<15 point increase from baseline, n(%)	21 (55.3)	6 (54.5)
Missing, n(%)	6 (15.8)	3 (27.3)
≥15 point increase from baseline, (95% CI)	28.9 (14.5, 43.4)	18.2 (0.0, 41.0)
Percentage difference (Vutrisiran - Patisiran), (95% CI)	10.766 (-16.205, 37.736)	
Odds ratio (Vutrisiran/Patisiran), (95% CI) [1]	1.833 (0.340, 9.886)	
Relative risk (Vutrisiran/Patisiran), (95% CI) [1]	1.592 (0.413, 6.135)	
P-value [2]	0.4992	
p-value of Treatment*FAP Stage [3]	0.5955	

Higher scores indicate higher quality of life (range = 0 to 100). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.
[1] Based on unstratified analysis.
In estimation of the odds ratio and relative risk, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the percentage difference or p-value.
[2] p-value based on the Wald test testing whether the relative risk equals to 1.
[3] p-value from a logistic regression using the penalized likelihood estimation (the FIRTH option) and with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

Alnylam Pharmaceuticals Inc.
ALN-TTRSC02-002

Table 7.4
EuroQol-Visual Analog Scale (EQ-VAS) Score
Binary Subgroup Analysis
mITT Population

Month 9

Analysis Visit Statistics	Vutrisiran (HELIOS-A) (N=122)	Patisiran (HELIOS-A) (N=42)
Cardiac Subpopulation		
Yes		
Patients included in analysis, N1	40	14
≥15 point increase from baseline, n(%)	10 (25.0)	2 (14.3)
<15 point increase from baseline, n(%)	27 (67.5)	12 (85.7)
Missing, n(%)	3 (7.5)	0
≥15 point increase from baseline, (95% CI)	25.0 (11.6, 38.4)	14.3 (0.0, 32.6)
Percentage difference (Vutrisiran – Patisiran), (95% CI)	10.714 (-12.003, 33.431)	
Odds ratio (Vutrisiran/Patisiran), (95% CI) [1]	2.000 (0.381, 10.511)	
Relative risk (Vutrisiran/Patisiran), (95% CI) [1]	1.750 (0.436, 7.032)	
P-value [2]	0.4303	

Higher scores indicate higher quality of life (range = 0 to 100). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.
[1] Based on unstratified analysis.
In estimation of the odds ratio and relative risk, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the percentage difference or p-value.
[2] p-value based on the Wald test testing whether the relative risk equals to 1.
[3] p-value from a logistic regression using the penalized likelihood estimation (the FIRTH option) and with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Alnylam Pharmaceuticals Inc.
ALN-TTRSC02-002

Table 7.4
EuroQol-Visual Analog Scale (EQ-VAS) Score
Binary Subgroup Analysis
mITT Population

Month 9

Analysis Visit Statistics	Vutrisiran (HELIOS-A) (N=122)	Patisiran (HELIOS-A) (N=42)
No		
Patients included in analysis, N1	82	28
≥15 point increase from baseline, n(%)	16 (19.5)	5 (17.9)
<15 point increase from baseline, n(%)	61 (74.4)	19 (67.9)
Missing, n(%)	5 (6.1)	4 (14.3)
≥15 point increase from baseline, (95% CI)	19.5 (10.9, 28.1)	17.9 (3.7, 32.0)
Percentage difference (Vutrisiran - Patisiran), (95% CI)	1.655 (-14.923, 18.233)	
Odds ratio (Vutrisiran/Patisiran), (95% CI) [1]	1.115 (0.367, 3.386)	
Relative risk (Vutrisiran/Patisiran), (95% CI) [1]	1.093 (0.441, 2.709)	
P-value [2]	0.8483	
p-value of Treatment*Cardiac Subpopulation [3]	0.6198	

Higher scores indicate higher quality of life (range = 0 to 100). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.
[1] Based on unstratified analysis.
In estimation of the odds ratio and relative risk, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the percentage difference or p-value.
[2] p-value based on the Wald test testing whether the relative risk equals to 1.
[3] p-value from a logistic regression using the penalized likelihood estimation (the FIRTH option) and with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Alnylam Pharmaceuticals Inc.
ALN-TTRSC02-002

Table 7.4
EuroQol-Visual Analog Scale (EQ-VAS) Score
Binary Subgroup Analysis
mITT Population

Month 18

Analysis Visit Statistics	Vutrisiran (HELIOS-A) (N=122)	Patisiran (HELIOS-A) (N=42)
Cardiac Subpopulation		
Yes		
Patients included in analysis, N1	40	14
≥15 point increase from baseline, n(%)	8 (20.0)	2 (14.3)
<15 point increase from baseline, n(%)	28 (70.0)	11 (78.6)
Missing, n(%)	4 (10.0)	1 (7.1)
≥15 point increase from baseline, (95% CI)	20.0 (7.6, 32.4)	14.3 (0.0, 32.6)
Percentage difference (Vutrisiran – Patisiran), (95% CI)	5.714 (-16.414, 27.842)	
Odds ratio (Vutrisiran/Patisiran), (95% CI) [1]	1.500 (0.278, 8.093)	
Relative risk (Vutrisiran/Patisiran), (95% CI) [1]	1.400 (0.337, 5.821)	
P-value [2]	0.6435	

Higher scores indicate higher quality of life (range = 0 to 100). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.
[1] Based on unstratified analysis.
In estimation of the odds ratio and relative risk, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the percentage difference or p-value.
[2] p-value based on the Wald test testing whether the relative risk equals to 1.
[3] p-value from a logistic regression using the penalized likelihood estimation (the FIRTH option) and with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Alnylam Pharmaceuticals Inc.
ALN-TTRSC02-002

Table 7.4
EuroQol-Visual Analog Scale (EQ-VAS) Score
Binary Subgroup Analysis
mITT Population

Month 18

Analysis Visit Statistics	Vutrisiran (HELIOS-A) (N=122)	Patisiran (HELIOS-A) (N=42)
No		
Patients included in analysis, N1	82	28
≥15 point increase from baseline, n(%)	19 (23.2)	2 (7.1)
<15 point increase from baseline, n(%)	57 (69.5)	22 (78.6)
Missing, n(%)	6 (7.3)	4 (14.3)
≥15 point increase from baseline, (95% CI)	23.2 (14.0, 32.3)	7.1 (0.0, 16.7)
Percentage difference (Vutrisiran - Patisiran), (95% CI)	16.028 (2.822, 29.234)	
Odds ratio (Vutrisiran/Patisiran), (95% CI) [1]	3.921 (0.852, 18.051)	
Relative risk (Vutrisiran/Patisiran), (95% CI) [1]	3.244 (0.806, 13.056)	
P-value [2]	0.0976	
p-value of Treatment*Cardiac Subpopulation [3]	0.4025	

Higher scores indicate higher quality of life (range = 0 to 100). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.
[1] Based on unstratified analysis.
In estimation of the odds ratio and relative risk, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the percentage difference or p-value.
[2] p-value based on the Wald test testing whether the relative risk equals to 1.
[3] p-value from a logistic regression using the penalized likelihood estimation (the FIRTH option) and with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Alnylam Pharmaceuticals Inc.
ALN-TTRSC02-002

Table 7.4
EuroQol-Visual Analog Scale (EQ-VAS) Score
Binary Subgroup Analysis
mITT Population

Month 9

Analysis Visit Statistics	Vutrisiran (HELIOS-A) (N=122)	Patisiran (HELIOS-A) (N=42)
Weight (kg)		
<65 kg		
Patients included in analysis, N1	46	15
≥15 point increase from baseline, n(%)	9 (19.6)	4 (26.7)
<15 point increase from baseline, n(%)	35 (76.1)	9 (60.0)
Missing, n(%)	2 (4.3)	2 (13.3)
≥15 point increase from baseline, (95% CI)	19.6 (8.1, 31.0)	26.7 (4.3, 49.0)
Percentage difference (Vutrisiran – Patisiran), (95% CI)	-7.101 (-32.246, 18.043)	
Odds ratio (Vutrisiran/Patisiran), (95% CI) [1]	0.669 (0.172, 2.597)	
Relative risk (Vutrisiran/Patisiran), (95% CI) [1]	0.734 (0.264, 2.042)	
P-value [2]	0.5532	

Higher scores indicate higher quality of life (range = 0 to 100). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.
[1] Based on unstratified analysis.
In estimation of the odds ratio and relative risk, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the percentage difference or p-value.
[2] p-value based on the Wald test testing whether the relative risk equals to 1.
[3] p-value from a logistic regression using the penalized likelihood estimation (the FIRTH option) and with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Alnylam Pharmaceuticals Inc.
ALN-TTRSC02-002

Table 7.4
EuroQol-Visual Analog Scale (EQ-VAS) Score
Binary Subgroup Analysis
mITT Population

Month 9

Analysis Visit Statistics	Vutrisiran (HELIOS-A) (N=122)	Patisiran (HELIOS-A) (N=42)
≥65 kg		
Patients included in analysis, N1	76	27
≥15 point increase from baseline, n(%)	17 (22.4)	3 (11.1)
<15 point increase from baseline, n(%)	53 (69.7)	22 (81.5)
Missing, n(%)	6 (7.9)	2 (7.4)
≥15 point increase from baseline, (95% CI)	22.4 (13.0, 31.7)	11.1 (0.0, 23.0)
Percentage difference (Vutrisiran - Patisiran), (95% CI)	11.257 (-3.852, 26.367)	
Odds ratio (Vutrisiran/Patisiran), (95% CI) [1]	2.305 (0.618, 8.594)	
Relative risk (Vutrisiran/Patisiran), (95% CI) [1]	2.013 (0.640, 6.333)	
P-value [2]	0.2315	
p-value of Treatment*Weight (kg) [3]	0.2169	

Higher scores indicate higher quality of life (range = 0 to 100). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.
[1] Based on unstratified analysis.
In estimation of the odds ratio and relative risk, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the percentage difference or p-value.
[2] p-value based on the Wald test testing whether the relative risk equals to 1.
[3] p-value from a logistic regression using the penalized likelihood estimation (the FIRTH option) and with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Alnylam Pharmaceuticals Inc.
ALN-TTRSC02-002

Table 7.4
EuroQol-Visual Analog Scale (EQ-VAS) Score
Binary Subgroup Analysis
mITT Population

Month 18

Analysis Visit Statistics	Vutrisiran (HELIOS-A) (N=122)	Patisiran (HELIOS-A) (N=42)
Weight (kg)		
<65 kg		
Patients included in analysis, N1	46	15
≥15 point increase from baseline, n(%)	11 (23.9)	2 (13.3)
<15 point increase from baseline, n(%)	31 (67.4)	12 (80.0)
Missing, n(%)	4 (8.7)	1 (6.7)
≥15 point increase from baseline, (95% CI)	23.9 (11.6, 36.2)	13.3 (0.0, 30.5)
Percentage difference (Vutrisiran – Patisiran), (95% CI)	10.580 (-10.583, 31.743)	
Odds ratio (Vutrisiran/Patisiran), (95% CI) [1]	2.043 (0.398, 10.485)	
Relative risk (Vutrisiran/Patisiran), (95% CI) [1]	1.793 (0.447, 7.196)	
P-value [2]	0.4099	

Higher scores indicate higher quality of life (range = 0 to 100). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.
[1] Based on unstratified analysis.
In estimation of the odds ratio and relative risk, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the percentage difference or p-value.
[2] p-value based on the Wald test testing whether the relative risk equals to 1.
[3] p-value from a logistic regression using the penalized likelihood estimation (the FIRTH option) and with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Alnylam Pharmaceuticals Inc.
ALN-TTRSC02-002

Table 7.4
EuroQol-Visual Analog Scale (EQ-VAS) Score
Binary Subgroup Analysis
mITT Population

Month 18

Analysis Visit Statistics	Vutrisiran (HELIOS-A) (N=122)	Patisiran (HELIOS-A) (N=42)
≥65 kg		
Patients included in analysis, N1	76	27
≥15 point increase from baseline, n(%)	16 (21.1)	2 (7.4)
<15 point increase from baseline, n(%)	54 (71.1)	21 (77.8)
Missing, n(%)	6 (7.9)	4 (14.8)
≥15 point increase from baseline, (95% CI)	21.1 (11.9, 30.2)	7.4 (0.0, 17.3)
Percentage difference (Vutrisiran - Patisiran), (95% CI)	13.645 (0.170, 27.121)	
Odds ratio (Vutrisiran/Patisiran), (95% CI) [1]	3.333 (0.713, 15.583)	
Relative risk (Vutrisiran/Patisiran), (95% CI) [1]	2.842 (0.699, 11.558)	
P-value [2]	0.1445	
p-value of Treatment*Weight (kg) [3]	0.6661	

Higher scores indicate higher quality of life (range = 0 to 100). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.
[1] Based on unstratified analysis.
In estimation of the odds ratio and relative risk, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the percentage difference or p-value.
[2] p-value based on the Wald test testing whether the relative risk equals to 1.
[3] p-value from a logistic regression using the penalized likelihood estimation (the FIRTH option) and with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Subgruppenanalysen zum Endpunkt „Veränderung der Mobilität gemessen anhand des FAP-Stadiums und des PND-Wertes“

FAP-Stadium

Alnylam Pharmaceuticals Inc.
ALN-TTRSC02-002

Table 8.2
Familial Amyloidotic Polyneuropathy (FAP) Stage: Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A)
Binary Subgroup Analysis
mITT Population

Month 9

Analysis Visit Statistics	Vutrisiran (HELIOS-A) (N=122)	Patisiran (HELIOS-A) (N=42)
Age (years)		
<65		
Patients included in analysis, N1	76	31
Improved, n(%)	1 (1.3)	2 (6.5)
No Change, n(%)	55 (72.4)	24 (77.4)
Worsened, n(%)	3 (3.9)	0
Missing, n(%)	17 (22.4)	5 (16.1)
Improved, (95% CI)	1.3 (0.0, 3.9)	6.5 (0.0, 15.1)
Percentage difference (Vutrisiran – Patisiran), (95% CI)	-5.136 (-14.155, 3.884)	
Odds ratio (Vutrisiran/Patisiran), (95% CI) [1]	0.193 (0.017, 2.215)	
Relative risk (Vutrisiran/Patisiran), (95% CI) [1]	0.204 (0.019, 2.168)	
P-value [2]	0.1874	

N1 = Patients with missing postbaseline values due to COVID-19 or after initiation of local standard treatment for hATTR amyloidosis were included in analysis.
[1] Based on unstratified analysis.
In estimation of the odds ratio and relative risk, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the percentage difference or p-value.
[2] p-value based on the Wald test testing whether the relative risk equals to 1.
[3] p-value from a logistic regression with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Alnylam Pharmaceuticals Inc.
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Table 8.2
Familial Amyloidotic Polyneuropathy (FAP) Stage: Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A)
Binary Subgroup Analysis
mITT Population

Month 9

Analysis Visit Statistics	Vutrisiran (HELIOS-A) (N=122)	Patisiran (HELIOS-A) (N=42)
≥65		
Patients included in analysis, N1	46	11
Improved, n(%)	3 (6.5)	0
No Change, n(%)	29 (63.0)	8 (72.7)
Worsened, n(%)	3 (6.5)	0
Missing, n(%)	11 (23.9)	3 (27.3)
Improved, (95% CI)	6.5 (0.0, 13.7)	0.0 (0.0, 0.0)
Percentage difference (Vutrisiran – Patisiran), (95% CI)	6.522 (-0.613, 13.657)	
Odds ratio (Vutrisiran/Patisiran), (95% CI) [1]	1.851 (0.089, 38.441)	
Relative risk (Vutrisiran/Patisiran), (95% CI) [1]	1.787 (0.099, 32.306)	
P-value [2]	0.6942	
p-value of Treatment*Age [3]	0.2847	

N1 = Patients with missing postbaseline values due to COVID-19 or after initiation of local standard treatment for hATTR amyloidosis were included in analysis.
[1] Based on unstratified analysis.
In estimation of the odds ratio and relative risk, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the percentage difference or p-value.
[2] p-value based on the Wald test testing whether the relative risk equals to 1.
[3] p-value from a logistic regression with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Table 8.2
Familial Amyloidotic Polyneuropathy (FAP) Stage: Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A)
Binary Subgroup Analysis
mITT Population

Month 18

Analysis Visit Statistics	Vutrisiran (HELIOS-A) (N=122)	Patisiran (HELIOS-A) (N=42)
Age (years)		
<65		
Patients included in analysis, N1	76	31
Improved, n(%)	2 (2.6)	1 (3.2)
No Change, n(%)	67 (88.2)	28 (90.3)
Worsened, n(%)	5 (6.6)	0
Missing, n(%)	2 (2.6)	2 (6.5)
Improved, (95% CI)	2.6 (0.0, 6.2)	3.2 (0.0, 9.4)
Percentage difference (Vutrisiran – Patisiran), (95% CI)	-0.594 (-7.780, 6.592)	
Odds ratio (Vutrisiran/Patisiran), (95% CI) [1]	0.811 (0.071, 9.281)	
Relative risk (Vutrisiran/Patisiran), (95% CI) [1]	0.816 (0.077, 8.673)	
P-value [2]	0.8659	

N1 = Patients with missing postbaseline values due to COVID-19 or after initiation of local standard treatment for hATTR amyloidosis were included in analysis.
[1] Based on unstratified analysis.
In estimation of the odds ratio and relative risk, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the percentage difference or p-value.
[2] p-value based on the Wald test testing whether the relative risk equals to 1.
[3] p-value from a logistic regression with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Table 8.2
Familial Amyloidotic Polyneuropathy (FAP) Stage: Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A)
Binary Subgroup Analysis
mITT Population

Month 18

Analysis Visit Statistics	Vutrisiran (HELIOS-A) (N=122)	Patisiran (HELIOS-A) (N=42)
≥65		
Patients included in analysis, N1	46	11
Improved, n(%)	3 (6.5)	0
No Change, n(%)	34 (73.9)	8 (72.7)
Worsened, n(%)	4 (8.7)	1 (9.1)
Missing, n(%)	5 (10.9)	2 (18.2)
Improved, (95% CI)	6.5 (0.0, 13.7)	0.0 (0.0, 0.0)
Percentage difference (Vutrisiran – Patisiran), (95% CI)	6.522 (-0.613, 13.657)	
Odds ratio (Vutrisiran/Patisiran), (95% CI) [1]	1.851 (0.089, 38.441)	
Relative risk (Vutrisiran/Patisiran), (95% CI) [1]	1.787 (0.099, 32.306)	
P-value [2]	0.6942	
p-value of Treatment*Age [3]	0.6056	

N1 = Patients with missing postbaseline values due to COVID-19 or after initiation of local standard treatment for hATTR amyloidosis were included in analysis.
[1] Based on unstratified analysis.
In estimation of the odds ratio and relative risk, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the percentage difference or p-value.
[2] p-value based on the Wald test testing whether the relative risk equals to 1.
[3] p-value from a logistic regression with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Alnylam Pharmaceuticals Inc.
ALN-TTRSC02-002

Table 8.2
Familial Amyloidotic Polyneuropathy (FAP) Stage: Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A)
Binary Subgroup Analysis
mITT Population

Month 9

Analysis Visit Statistics	Vutrisiran (HELIOS-A) (N=122)	Patisiran (HELIOS-A) (N=42)
Sex		
Male		
Patients included in analysis, N1	79	27
Improved, n(%)	3 (3.8)	2 (7.4)
No Change, n(%)	53 (67.1)	20 (74.1)
Worsened, n(%)	5 (6.3)	0
Missing, n(%)	18 (22.8)	5 (18.5)
Improved, (95% CI)	3.8 (0.0, 8.0)	7.4 (0.0, 17.3)
Percentage difference (Vutrisiran – Patisiran), (95% CI)	-3.610 (-14.350, 7.130)	
Odds ratio (Vutrisiran/Patisiran), (95% CI) [1]	0.493 (0.078, 3.124)	
Relative risk (Vutrisiran/Patisiran), (95% CI) [1]	0.513 (0.090, 2.906)	
P-value [2]	0.4504	

N1 = Patients with missing postbaseline values due to COVID-19 or after initiation of local standard treatment for hATTR amyloidosis were included in analysis.
[1] Based on unstratified analysis.
In estimation of the odds ratio and relative risk, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the percentage difference or p-value.
[2] p-value based on the Wald test testing whether the relative risk equals to 1.
[3] p-value from a logistic regression with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Alnylam Pharmaceuticals Inc.
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Table 8.2
Familial Amyloidotic Polyneuropathy (FAP) Stage: Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A)
Binary Subgroup Analysis
mITT Population

Month 9

Analysis Visit Statistics	Vutrisiran (HELIOS-A) (N=122)	Patisiran (HELIOS-A) (N=42)
Female		
Patients included in analysis, N1	43	15
Improved, n(%)	1 (2.3)	0
No Change, n(%)	31 (72.1)	12 (80.0)
Worsened, n(%)	1 (2.3)	0
Missing, n(%)	10 (23.3)	3 (20.0)
Improved, (95% CI)	2.3 (0.0, 6.8)	0.0 (0.0, 0.0)
Percentage difference (Vutrisiran – Patisiran), (95% CI)	2.326 (-2.179, 6.830)	
Odds ratio (Vutrisiran/Patisiran), (95% CI) [1]	1.094 (0.042, 28.303)	
Relative risk (Vutrisiran/Patisiran), (95% CI) [1]	1.091 (0.047, 25.433)	
P-value [2]	0.9568	
p-value of Treatment*Sex [3]	0.6563	

N1 = Patients with missing postbaseline values due to COVID-19 or after initiation of local standard treatment for hATTR amyloidosis were included in analysis.
[1] Based on unstratified analysis.
In estimation of the odds ratio and relative risk, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the percentage difference or p-value.
[2] p-value based on the Wald test testing whether the relative risk equals to 1.
[3] p-value from a logistic regression with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Table 8.2
Familial Amyloidotic Polyneuropathy (FAP) Stage: Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A)
Binary Subgroup Analysis
mITT Population

Month 18

Analysis Visit Statistics	Vutrisiran (HELIOS-A) (N=122)	Patisiran (HELIOS-A) (N=42)
Sex		
Male		
Patients included in analysis, N1	79	27
Improved, n(%)	3 (3.8)	1 (3.7)
No Change, n(%)	64 (81.0)	21 (77.8)
Worsened, n(%)	7 (8.9)	1 (3.7)
Missing, n(%)	5 (6.3)	4 (14.8)
Improved, (95% CI)	3.8 (0.0, 8.0)	3.7 (0.0, 10.8)
Percentage difference (Vutrisiran – Patisiran), (95% CI)	0.094 (-8.183, 8.371)	
Odds ratio (Vutrisiran/Patisiran), (95% CI) [1]	1.026 (0.102, 10.304)	
Relative risk (Vutrisiran/Patisiran), (95% CI) [1]	1.025 (0.111, 9.446)	
P-value [2]	0.9824	

N1 = Patients with missing postbaseline values due to COVID-19 or after initiation of local standard treatment for hATTR amyloidosis were included in analysis.
[1] Based on unstratified analysis.
In estimation of the odds ratio and relative risk, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the percentage difference or p-value.
[2] p-value based on the Wald test testing whether the relative risk equals to 1.
[3] p-value from a logistic regression with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Table 8.2
Familial Amyloidotic Polyneuropathy (FAP) Stage: Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A)
Binary Subgroup Analysis
mITT Population

Month 18

Analysis Visit Statistics	Vutrisiran (HELIOS-A) (N=122)	Patisiran (HELIOS-A) (N=42)
Female		
Patients included in analysis, N1	43	15
Improved, n(%)	2 (4.7)	0
No Change, n(%)	37 (86.0)	15 (100.0)
Worsened, n(%)	2 (4.7)	0
Missing, n(%)	2 (4.7)	0
Improved, (95% CI)	4.7 (0.0, 10.9)	0.0 (0.0, 0.0)
Percentage difference (Vutrisiran – Patisiran), (95% CI)	4.651 (-1.643, 10.946)	
Odds ratio (Vutrisiran/Patisiran), (95% CI) [1]	1.867 (0.085, 41.120)	
Relative risk (Vutrisiran/Patisiran), (95% CI) [1]	1.818 (0.092, 35.866)	
P-value [2]	0.6944	
p-value of Treatment*Sex [3]	0.6620	

N1 = Patients with missing postbaseline values due to COVID-19 or after initiation of local standard treatment for hATTR amyloidosis were included in analysis.
[1] Based on unstratified analysis.
In estimation of the odds ratio and relative risk, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the percentage difference or p-value.
[2] p-value based on the Wald test testing whether the relative risk equals to 1.
[3] p-value from a logistic regression with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Familial Amyloidotic Polyneuropathy (FAP) Stage: Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A)
Binary Subgroup Analysis
mITT Population

Month 9

Analysis Visit Statistics	Vutrisiran (HELIOS-A) (N=122)	Patisiran (HELIOS-A) (N=42)
Race		
White		
Patients included in analysis, N1	86	29
Improved, n(%)	2 (2.3)	1 (3.4)
No Change, n(%)	61 (70.9)	24 (82.8)
Worsened, n(%)	4 (4.7)	0
Missing, n(%)	19 (22.1)	4 (13.8)
Improved, (95% CI)	2.3 (0.0, 5.5)	3.4 (0.0, 10.1)
Percentage difference (Vutrisiran – Patisiran), (95% CI)	-1.123 (-8.488, 6.243)	
Odds ratio (Vutrisiran/Patisiran), (95% CI) [1]	0.667 (0.058, 7.635)	
Relative risk (Vutrisiran/Patisiran), (95% CI) [1]	0.674 (0.063, 7.166)	
P-value [2]	0.7439	

N1 = Patients with missing postbaseline values due to COVID-19 or after initiation of local standard treatment for hATTR amyloidosis were included in analysis.
[1] Based on unstratified analysis.
In estimation of the odds ratio and relative risk, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the percentage difference or p-value.
[2] p-value based on the Wald test testing whether the relative risk equals to 1.
[3] p-value from a logistic regression with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Table 8.2
Familial Amyloidotic Polyneuropathy (FAP) Stage: Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A)
Binary Subgroup Analysis
mITT Population

Month 9

Analysis Visit Statistics	Vutrisiran (HELIOS-A) (N=122)	Patisiran (HELIOS-A) (N=42)
All Other Races		
Patients included in analysis, N1	36	13
Improved, n(%)	2 (5.6)	1 (7.7)
No Change, n(%)	23 (63.9)	8 (61.5)
Worsened, n(%)	2 (5.6)	0
Missing, n(%)	9 (25.0)	4 (30.8)
Improved, (95% CI)	5.6 (0.0, 13.0)	7.7 (0.0, 22.2)
Percentage difference (Vutrisiran – Patisiran), (95% CI)	-2.137 (-18.440, 14.167)	
Odds ratio (Vutrisiran/Patisiran), (95% CI) [1]	0.706 (0.059, 8.506)	
Relative risk (Vutrisiran/Patisiran), (95% CI) [1]	0.722 (0.071, 7.314)	
P-value [2]	0.7829	
p-value of Treatment*Race [3]	0.9632	

N1 = Patients with missing postbaseline values due to COVID-19 or after initiation of local standard treatment for hATTR amyloidosis were included in analysis.
[1] Based on unstratified analysis.
In estimation of the odds ratio and relative risk, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the percentage difference or p-value.
[2] p-value based on the Wald test testing whether the relative risk equals to 1.
[3] p-value from a logistic regression with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Table 8.2
Familial Amyloidotic Polyneuropathy (FAP) Stage: Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A)
Binary Subgroup Analysis
mITT Population

Month 18

Analysis Visit Statistics	Vutrisiran (HELIOS-A) (N=122)	Patisiran (HELIOS-A) (N=42)
Race		
White		
Patients included in analysis, N1	86	29
Improved, n(%)	2 (2.3)	0
No Change, n(%)	74 (86.0)	27 (93.1)
Worsened, n(%)	6 (7.0)	0
Missing, n(%)	4 (4.7)	2 (6.9)
Improved, (95% CI)	2.3 (0.0, 5.5)	0.0 (0.0, 0.0)
Percentage difference (Vutrisiran – Patisiran), (95% CI)	2.326 (-0.860, 5.511)	
Odds ratio (Vutrisiran/Patisiran), (95% CI) [1]	1.746 (0.081, 37.421)	
Relative risk (Vutrisiran/Patisiran), (95% CI) [1]	1.724 (0.085, 34.904)	
P-value [2]	0.7226	

N1 = Patients with missing postbaseline values due to COVID-19 or after initiation of local standard treatment for hATTR amyloidosis were included in analysis.
[1] Based on unstratified analysis.
In estimation of the odds ratio and relative risk, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the percentage difference or p-value.
[2] p-value based on the Wald test testing whether the relative risk equals to 1.
[3] p-value from a logistic regression with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Table 8.2
Familial Amyloidotic Polyneuropathy (FAP) Stage: Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A)
Binary Subgroup Analysis
mITT Population

Month 18

Analysis Visit Statistics	Vutrisiran (HELIOS-A) (N=122)	Patisiran (HELIOS-A) (N=42)
All Other Races		
Patients included in analysis, N1	36	13
Improved, n(%)	3 (8.3)	1 (7.7)
No Change, n(%)	27 (75.0)	9 (69.2)
Worsened, n(%)	3 (8.3)	1 (7.7)
Missing, n(%)	3 (8.3)	2 (15.4)
Improved, (95% CI)	8.3 (0.0, 17.4)	7.7 (0.0, 22.2)
Percentage difference (Vutrisiran – Patisiran), (95% CI)	0.641 (-16.427, 17.709)	
Odds ratio (Vutrisiran/Patisiran), (95% CI) [1]	1.091 (0.103, 11.527)	
Relative risk (Vutrisiran/Patisiran), (95% CI) [1]	1.083 (0.123, 9.512)	
P-value [2]	0.9424	
p-value of Treatment*Race [3]	0.7157	

N1 = Patients with missing postbaseline values due to COVID-19 or after initiation of local standard treatment for hATTR amyloidosis were included in analysis.
[1] Based on unstratified analysis.
In estimation of the odds ratio and relative risk, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the percentage difference or p-value.
[2] p-value based on the Wald test testing whether the relative risk equals to 1.
[3] p-value from a logistic regression with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Table 8.2
Familial Amyloidotic Polyneuropathy (FAP) Stage: Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A)
Binary Subgroup Analysis
mITT Population

Month 9

Analysis Visit Statistics	Vutrisiran (HELIOS-A) (N=122)	Patisiran (HELIOS-A) (N=42)
Region		
North America		
Patients included in analysis, N1	27	8
Improved, n(%)	1 (3.7)	0
No Change, n(%)	15 (55.6)	5 (62.5)
Worsened, n(%)	0	0
Missing, n(%)	11 (40.7)	3 (37.5)
Improved, (95% CI)	3.7 (0.0, 10.8)	0.0 (0.0, 0.0)
Percentage difference (Vutrisiran – Patisiran), (95% CI)	3.704 (-3.420, 10.827)	
Odds ratio (Vutrisiran/Patisiran), (95% CI) [1]	0.962 (0.036, 25.895)	
Relative risk (Vutrisiran/Patisiran), (95% CI) [1]	0.964 (0.043, 21.647)	
P-value [2]	0.9817	

N1 = Patients with missing postbaseline values due to COVID-19 or after initiation of local standard treatment for hATTR amyloidosis were included in analysis.
[1] Based on unstratified analysis.
In estimation of the odds ratio and relative risk, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the percentage difference or p-value.
[2] p-value based on the Wald test testing whether the relative risk equals to 1.
[3] p-value from a logistic regression with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Binary Subgroup Analysis
mITT Population

Month 9

Analysis Visit Statistics	Vutrisiran (HELIOS-A) (N=122)	Patisiran (HELIOS-A) (N=42)
Western Europe		
Patients included in analysis, N1	42	20
Improved, n(%)	2 (4.8)	1 (5.0)
No Change, n(%)	33 (78.6)	15 (75.0)
Worsened, n(%)	4 (9.5)	0
Missing, n(%)	3 (7.1)	4 (20.0)
Improved, (95% CI)	4.8 (0.0, 11.2)	5.0 (0.0, 14.6)
Percentage difference (Vutrisiran – Patisiran), (95% CI)	-0.238 (-11.758, 11.282)	
Odds ratio (Vutrisiran/Patisiran), (95% CI) [1]	0.950 (0.081, 11.139)	
Relative risk (Vutrisiran/Patisiran), (95% CI) [1]	0.952 (0.092, 9.893)	
P-value [2]	0.9674	

N1 = Patients with missing postbaseline values due to COVID-19 or after initiation of local standard treatment for hATTR amyloidosis were included in analysis.
[1] Based on unstratified analysis.
In estimation of the odds ratio and relative risk, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the percentage difference or p-value.
[2] p-value based on the Wald test testing whether the relative risk equals to 1.
[3] p-value from a logistic regression with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Binary Subgroup Analysis
mITT Population

Month 9

Analysis Visit Statistics	Vutrisiran (HELIOS-A) (N=122)	Patisiran (HELIOS-A) (N=42)
Rest of World		
Patients included in analysis, N1	53	14
Improved, n(%)	1 (1.9)	1 (7.1)
No Change, n(%)	36 (67.9)	12 (85.7)
Worsened, n(%)	2 (3.8)	0
Missing, n(%)	14 (26.4)	1 (7.1)
Improved, (95% CI)	1.9 (0.0, 5.5)	7.1 (0.0, 20.6)
Percentage difference (Vutrisiran – Patisiran), (95% CI)	-5.256 (-19.235, 8.723)	
Odds ratio (Vutrisiran/Patisiran), (95% CI) [1]	0.250 (0.015, 4.269)	
Relative risk (Vutrisiran/Patisiran), (95% CI) [1]	0.264 (0.018, 3.964)	
P-value [2]	0.3354	
p-value of Treatment*Region [3]	0.7379	

N1 = Patients with missing postbaseline values due to COVID-19 or after initiation of local standard treatment for hATTR amyloidosis were included in analysis.
[1] Based on unstratified analysis.
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[2] p-value based on the Wald test testing whether the relative risk equals to 1.
[3] p-value from a logistic regression with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Binary Subgroup Analysis
mITT Population

Month 18

Analysis Visit Statistics	Vutrisiran (HELIOS-A) (N=122)	Patisiran (HELIOS-A) (N=42)
Region		
North America		
Patients included in analysis, N1	27	8
Improved, n(%)	1 (3.7)	0
No Change, n(%)	23 (85.2)	7 (87.5)
Worsened, n(%)	1 (3.7)	0
Missing, n(%)	2 (7.4)	1 (12.5)
Improved, (95% CI)	3.7 (0.0, 10.8)	0.0 (0.0, 0.0)
Percentage difference (Vutrisiran – Patisiran), (95% CI)	3.704 (-3.420, 10.827)	
Odds ratio (Vutrisiran/Patisiran), (95% CI) [1]	0.962 (0.036, 25.895)	
Relative risk (Vutrisiran/Patisiran), (95% CI) [1]	0.964 (0.043, 21.647)	
P-value [2]	0.9817	

N1 = Patients with missing postbaseline values due to COVID-19 or after initiation of local standard treatment for hATTR amyloidosis were included in analysis.
[1] Based on unstratified analysis.
In estimation of the odds ratio and relative risk, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the percentage difference or p-value.
[2] p-value based on the Wald test testing whether the relative risk equals to 1.
[3] p-value from a logistic regression with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Binary Subgroup Analysis
mITT Population

Month 18

Analysis Visit Statistics	Vutrisiran (HELIOS-A) (N=122)	Patisiran (HELIOS-A) (N=42)
Western Europe		
Patients included in analysis, N1	42	20
Improved, n(%)	2 (4.8)	0
No Change, n(%)	35 (83.3)	18 (90.0)
Worsened, n(%)	3 (7.1)	0
Missing, n(%)	2 (4.8)	2 (10.0)
Improved, (95% CI)	4.8 (0.0, 11.2)	0.0 (0.0, 0.0)
Percentage difference (Vutrisiran – Patisiran), (95% CI)	4.762 (-1.679, 11.202)	
Odds ratio (Vutrisiran/Patisiran), (95% CI) [1]	2.531 (0.116, 55.205)	
Relative risk (Vutrisiran/Patisiran), (95% CI) [1]	2.442 (0.123, 48.616)	
P-value [2]	0.5586	

N1 = Patients with missing postbaseline values due to COVID-19 or after initiation of local standard treatment for hATTR amyloidosis were included in analysis.
[1] Based on unstratified analysis.
In estimation of the odds ratio and relative risk, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the percentage difference or p-value.
[2] p-value based on the Wald test testing whether the relative risk equals to 1.
[3] p-value from a logistic regression with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Binary Subgroup Analysis
mITT Population

Month 18

Analysis Visit Statistics	Vutrisiran (HELIOS-A) (N=122)	Patisiran (HELIOS-A) (N=42)
Rest of World		
Patients included in analysis, N1	53	14
Improved, n(%)	2 (3.8)	1 (7.1)
No Change, n(%)	43 (81.1)	11 (78.6)
Worsened, n(%)	5 (9.4)	1 (7.1)
Missing, n(%)	3 (5.7)	1 (7.1)
Improved, (95% CI)	3.8 (0.0, 8.9)	7.1 (0.0, 20.6)
Percentage difference (Vutrisiran – Patisiran), (95% CI)	-3.369 (-17.802, 11.064)	
Odds ratio (Vutrisiran/Patisiran), (95% CI) [1]	0.510 (0.043, 6.066)	
Relative risk (Vutrisiran/Patisiran), (95% CI) [1]	0.528 (0.052, 5.414)	
P-value [2]	0.5910	
p-value of Treatment*Region [3]	0.6625	

N1 = Patients with missing postbaseline values due to COVID-19 or after initiation of local standard treatment for hATTR amyloidosis were included in analysis.
[1] Based on unstratified analysis.
In estimation of the odds ratio and relative risk, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the percentage difference or p-value.
[2] p-value based on the Wald test testing whether the relative risk equals to 1.
[3] p-value from a logistic regression with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

Alnylam Pharmaceuticals Inc.
ALN-TTRSC02-002

Table 8.2
Familial Amyloidotic Polyneuropathy (FAP) Stage: Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A)
Binary Subgroup Analysis
mITT Population

Month 9

Analysis Visit Statistics	Vutrisiran (HELIOS-A) (N=122)	Patisiran (HELIOS-A) (N=42)
Baseline NIS		
<50		
Patients included in analysis, N1	78	27
Improved, n(%)	3 (3.8)	0
No Change, n(%)	53 (67.9)	21 (77.8)
Worsened, n(%)	2 (2.6)	0
Missing, n(%)	20 (25.6)	6 (22.2)
Improved, (95% CI)	3.8 (0.0, 8.1)	0.0 (0.0, 0.0)
Percentage difference (Vutrisiran – Patisiran), (95% CI)	3.846 (-0.422, 8.114)	
Odds ratio (Vutrisiran/Patisiran), (95% CI) [1]	2.550 (0.128, 50.965)	
Relative risk (Vutrisiran/Patisiran), (95% CI) [1]	2.481 (0.132, 46.541)	
P-value [2]	0.5435	

N1 = Patients with missing postbaseline values due to COVID-19 or after initiation of local standard treatment for hATTR amyloidosis were included in analysis.
[1] Based on unstratified analysis.
In estimation of the odds ratio and relative risk, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the percentage difference or p-value.
[2] p-value based on the Wald test testing whether the relative risk equals to 1.
[3] p-value from a logistic regression with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

Alnylam Pharmaceuticals Inc.
ALN-TTRSC02-002

Table 8.2
Familial Amyloidotic Polyneuropathy (FAP) Stage: Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A)
Binary Subgroup Analysis
mITT Population

Month 9

Analysis Visit Statistics	Vutrisiran (HELIOS-A) (N=122)	Patisiran (HELIOS-A) (N=42)
≥50		
Patients included in analysis, N1	44	15
Improved, n(%)	1 (2.3)	2 (13.3)
No Change, n(%)	31 (70.5)	11 (73.3)
Worsened, n(%)	4 (9.1)	0
Missing, n(%)	8 (18.2)	2 (13.3)
Improved, (95% CI)	2.3 (0.0, 6.7)	13.3 (0.0, 30.5)
Percentage difference (Vutrisiran – Patisiran), (95% CI)	-11.061 (-28.818, 6.697)	
Odds ratio (Vutrisiran/Patisiran), (95% CI) [1]	0.151 (0.013, 1.804)	
Relative risk (Vutrisiran/Patisiran), (95% CI) [1]	0.170 (0.017, 1.748)	
P-value [2]	0.1363	
p-value of Treatment*Baseline NIS [3]	0.1693	

N1 = Patients with missing postbaseline values due to COVID-19 or after initiation of local standard treatment for hATTR amyloidosis were included in analysis.
[1] Based on unstratified analysis.
In estimation of the odds ratio and relative risk, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the percentage difference or p-value.
[2] p-value based on the Wald test testing whether the relative risk equals to 1.
[3] p-value from a logistic regression with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Alnylam Pharmaceuticals Inc.
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Table 8.2
Familial Amyloidotic Polyneuropathy (FAP) Stage: Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A)
Binary Subgroup Analysis
mITT Population

Month 18

Analysis Visit Statistics	Vutrisiran (HELIOS-A) (N=122)	Patisiran (HELIOS-A) (N=42)
Baseline NIS		
<50		
Patients included in analysis, N1	78	27
Improved, n(%)	4 (5.1)	0
No Change, n(%)	68 (87.2)	26 (96.3)
Worsened, n(%)	3 (3.8)	0
Missing, n(%)	3 (3.8)	1 (3.7)
Improved, (95% CI)	5.1 (0.2, 10.0)	0.0 (0.0, 0.0)
Percentage difference (Vutrisiran – Patisiran), (95% CI)	5.128 (0.233, 10.023)	
Odds ratio (Vutrisiran/Patisiran), (95% CI) [1]	3.322 (0.173, 63.746)	
Relative risk (Vutrisiran/Patisiran), (95% CI) [1]	3.190 (0.177, 57.383)	
P-value [2]	0.4314	

N1 = Patients with missing postbaseline values due to COVID-19 or after initiation of local standard treatment for hATTR amyloidosis were included in analysis.
[1] Based on unstratified analysis.
In estimation of the odds ratio and relative risk, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the percentage difference or p-value.
[2] p-value based on the Wald test testing whether the relative risk equals to 1.
[3] p-value from a logistic regression with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Table 8.2
Familial Amyloidotic Polyneuropathy (FAP) Stage: Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A)
Binary Subgroup Analysis
mITT Population

Month 18

Analysis Visit Statistics	Vutrisiran (HELIOS-A) (N=122)	Patisiran (HELIOS-A) (N=42)
≥50		
Patients included in analysis, N1	44	15
Improved, n(%)	1 (2.3)	1 (6.7)
No Change, n(%)	33 (75.0)	10 (66.7)
Worsened, n(%)	6 (13.6)	1 (6.7)
Missing, n(%)	4 (9.1)	3 (20.0)
Improved, (95% CI)	2.3 (0.0, 6.7)	6.7 (0.0, 19.3)
Percentage difference (Vutrisiran – Patisiran), (95% CI)	-4.394 (-17.763, 8.975)	
Odds ratio (Vutrisiran/Patisiran), (95% CI) [1]	0.326 (0.019, 5.554)	
Relative risk (Vutrisiran/Patisiran), (95% CI) [1]	0.341 (0.023, 5.119)	
P-value [2]	0.4362	
p-value of Treatment*Baseline NIS [3]	0.2407	

N1 = Patients with missing postbaseline values due to COVID-19 or after initiation of local standard treatment for hATTR amyloidosis were included in analysis.
[1] Based on unstratified analysis.
In estimation of the odds ratio and relative risk, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the percentage difference or p-value.
[2] p-value based on the Wald test testing whether the relative risk equals to 1.
[3] p-value from a logistic regression with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Table 8.2
Familial Amyloidotic Polyneuropathy (FAP) Stage: Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A)
Binary Subgroup Analysis
mITT Population

Month 9

Analysis Visit Statistics	Vutrisiran (HELIOS-A) (N=122)	Patisiran (HELIOS-A) (N=42)
Previous Tetramer Stabilizer Use		
Yes		
Patients included in analysis, N1	75	33
Improved, n(%)	1 (1.3)	2 (6.1)
No Change, n(%)	63 (84.0)	27 (81.8)
Worsened, n(%)	4 (5.3)	0
Missing, n(%)	7 (9.3)	4 (12.1)
Improved, (95% CI)	1.3 (0.0, 3.9)	6.1 (0.0, 14.2)
Percentage difference (Vutrisiran – Patisiran), (95% CI)	-4.727 (-13.272, 3.817)	
Odds ratio (Vutrisiran/Patisiran), (95% CI) [1]	0.209 (0.018, 2.395)	
Relative risk (Vutrisiran/Patisiran), (95% CI) [1]	0.220 (0.021, 2.342)	
P-value [2]	0.2096	

N1 = Patients with missing postbaseline values due to COVID-19 or after initiation of local standard treatment for hATTR amyloidosis were included in analysis.
[1] Based on unstratified analysis.
In estimation of the odds ratio and relative risk, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the percentage difference or p-value.
[2] p-value based on the Wald test testing whether the relative risk equals to 1.
[3] p-value from a logistic regression with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Table 8.2
Familial Amyloidotic Polyneuropathy (FAP) Stage: Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A)
Binary Subgroup Analysis
mITT Population

Month 9

Analysis Visit Statistics	Vutrisiran (HELIOS-A) (N=122)	Patisiran (HELIOS-A) (N=42)
No		
Patients included in analysis, N1	47	9
Improved, n(%)	3 (6.4)	0
No Change, n(%)	21 (44.7)	5 (55.6)
Worsened, n(%)	2 (4.3)	0
Missing, n(%)	21 (44.7)	4 (44.4)
Improved, (95% CI)	6.4 (0.0, 13.4)	0.0 (0.0, 0.0)
Percentage difference (Vutrisiran – Patisiran), (95% CI)	6.383 (-0.606, 13.372)	
Odds ratio (Vutrisiran/Patisiran), (95% CI) [1]	1.494 (0.071, 31.393)	
Relative risk (Vutrisiran/Patisiran), (95% CI) [1]	1.458 (0.082, 26.078)	
P-value [2]	0.7976	
p-value of Treatment*Previous Tetramer Stabilizer Use [3]	0.3623	

N1 = Patients with missing postbaseline values due to COVID-19 or after initiation of local standard treatment for hATTR amyloidosis were included in analysis.
[1] Based on unstratified analysis.
In estimation of the odds ratio and relative risk, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the percentage difference or p-value.
[2] p-value based on the Wald test testing whether the relative risk equals to 1.
[3] p-value from a logistic regression with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Familial Amyloidotic Polyneuropathy (FAP) Stage: Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A)
Binary Subgroup Analysis
mITT Population

Month 18

Analysis Visit Statistics	Vutrisiran (HELIOS-A) (N=122)	Patisiran (HELIOS-A) (N=42)
Previous Tetramer Stabilizer Use		
Yes		
Patients included in analysis, N1	75	33
Improved, n(%)	1 (1.3)	1 (3.0)
No Change, n(%)	63 (84.0)	29 (87.9)
Worsened, n(%)	7 (9.3)	1 (3.0)
Missing, n(%)	4 (5.3)	2 (6.1)
Improved, (95% CI)	1.3 (0.0, 3.9)	3.0 (0.0, 8.9)
Percentage difference (Vutrisiran – Patisiran), (95% CI)	-1.697 (-8.096, 4.702)	
Odds ratio (Vutrisiran/Patisiran), (95% CI) [1]	0.432 (0.026, 7.130)	
Relative risk (Vutrisiran/Patisiran), (95% CI) [1]	0.440 (0.028, 6.824)	
P-value [2]	0.5572	

N1 = Patients with missing postbaseline values due to COVID-19 or after initiation of local standard treatment for hATTR amyloidosis were included in analysis.
[1] Based on unstratified analysis.
In estimation of the odds ratio and relative risk, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the percentage difference or p-value.
[2] p-value based on the Wald test testing whether the relative risk equals to 1.
[3] p-value from a logistic regression with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Familial Amyloidotic Polyneuropathy (FAP) Stage: Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A)
Binary Subgroup Analysis
mITT Population

Month 18

Analysis Visit Statistics	Vutrisiran (HELIOS-A) (N=122)	Patisiran (HELIOS-A) (N=42)
No		
Patients included in analysis, N1	47	9
Improved, n(%)	4 (8.5)	0
No Change, n(%)	38 (80.9)	7 (77.8)
Worsened, n(%)	2 (4.3)	0
Missing, n(%)	3 (6.4)	2 (22.2)
Improved, (95% CI)	8.5 (0.5, 16.5)	0.0 (0.0, 0.0)
Percentage difference (Vutrisiran – Patisiran), (95% CI)	8.511 (0.533, 16.488)	
Odds ratio (Vutrisiran/Patisiran), (95% CI) [1]	1.966 (0.097, 39.671)	
Relative risk (Vutrisiran/Patisiran), (95% CI) [1]	1.875 (0.109, 32.130)	
P-value [2]	0.6646	
p-value of Treatment*Previous Tetramer Stabilizer Use [3]	0.4515	

N1 = Patients with missing postbaseline values due to COVID-19 or after initiation of local standard treatment for hATTR amyloidosis were included in analysis.
[1] Based on unstratified analysis.
In estimation of the odds ratio and relative risk, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the percentage difference or p-value.
[2] p-value based on the Wald test testing whether the relative risk equals to 1.
[3] p-value from a logistic regression with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Binary Subgroup Analysis
mITT Population

Month 9

Analysis Visit Statistics	Vutrisiran (HELIOS-A) (N=122)	Patisiran (HELIOS-A) (N=42)
Genotype		
V30M		
Patients included in analysis, N1	54	20
Improved, n(%)	0	1 (5.0)
No Change, n(%)	43 (79.6)	18 (90.0)
Worsened, n(%)	3 (5.6)	0
Missing, n(%)	8 (14.8)	1 (5.0)
Improved, (95% CI)	0.0 (0.0, 0.0)	5.0 (0.0, 14.6)
Percentage difference (Vutrisiran – Patisiran), (95% CI)	-5.000 (-14.552, 4.552)	
Odds ratio (Vutrisiran/Patisiran), (95% CI) [1]	0.119 (0.005, 3.052)	
Relative risk (Vutrisiran/Patisiran), (95% CI) [1]	0.127 (0.005, 3.003)	
P-value [2]	0.2012	

N1 = Patients with missing postbaseline values due to COVID-19 or after initiation of local standard treatment for hATTR amyloidosis were included in analysis.
[1] Based on unstratified analysis.
In estimation of the odds ratio and relative risk, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the percentage difference or p-value.
[2] p-value based on the Wald test testing whether the relative risk equals to 1.
[3] p-value from a logistic regression with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Binary Subgroup Analysis
mITT Population

Month 9

Analysis Visit Statistics	Vutrisiran (HELIOS-A) (N=122)	Patisiran (HELIOS-A) (N=42)
non-V30M		
Patients included in analysis, N1	68	22
Improved, n(%)	4 (5.9)	1 (4.5)
No Change, n(%)	41 (60.3)	14 (63.6)
Worsened, n(%)	3 (4.4)	0
Missing, n(%)	20 (29.4)	7 (31.8)
Improved, (95% CI)	5.9 (0.3, 11.5)	4.5 (0.0, 13.2)
Percentage difference (Vutrisiran – Patisiran), (95% CI)	1.337 (-9.009, 11.683)	
Odds ratio (Vutrisiran/Patisiran), (95% CI) [1]	1.313 (0.139, 12.404)	
Relative risk (Vutrisiran/Patisiran), (95% CI) [1]	1.294 (0.153, 10.976)	
P-value [2]	0.8131	
p-value of Treatment*Genotype [3]	0.2751	

N1 = Patients with missing postbaseline values due to COVID-19 or after initiation of local standard treatment for hATTR amyloidosis were included in analysis.
[1] Based on unstratified analysis.
In estimation of the odds ratio and relative risk, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the percentage difference or p-value.
[2] p-value based on the Wald test testing whether the relative risk equals to 1.
[3] p-value from a logistic regression with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Binary Subgroup Analysis
mITT Population

Month 18

Analysis Visit Statistics	Vutrisiran (HELIOS-A) (N=122)	Patisiran (HELIOS-A) (N=42)
Genotype		
V30M		
Patients included in analysis, N1	54	20
Improved, n(%)	2 (3.7)	0
No Change, n(%)	46 (85.2)	19 (95.0)
Worsened, n(%)	4 (7.4)	1 (5.0)
Missing, n(%)	2 (3.7)	0
Improved, (95% CI)	3.7 (0.0, 8.7)	0.0 (0.0, 0.0)
Percentage difference (Vutrisiran – Patisiran), (95% CI)	3.704 (-1.333, 8.741)	
Odds ratio (Vutrisiran/Patisiran), (95% CI) [1]	1.952 (0.090, 42.437)	
Relative risk (Vutrisiran/Patisiran), (95% CI) [1]	1.909 (0.096, 38.133)	
P-value [2]	0.6721	

N1 = Patients with missing postbaseline values due to COVID-19 or after initiation of local standard treatment for hATTR amyloidosis were included in analysis.
[1] Based on unstratified analysis.
In estimation of the odds ratio and relative risk, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the percentage difference or p-value.
[2] p-value based on the Wald test testing whether the relative risk equals to 1.
[3] p-value from a logistic regression with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Binary Subgroup Analysis
mITT Population

Month 18

Analysis Visit Statistics	Vutrisiran (HELIOS-A) (N=122)	Patisiran (HELIOS-A) (N=42)
non-V30M		
Patients included in analysis, N1	68	22
Improved, n(%)	3 (4.4)	1 (4.5)
No Change, n(%)	55 (80.9)	17 (77.3)
Worsened, n(%)	5 (7.4)	0
Missing, n(%)	5 (7.4)	4 (18.2)
Improved, (95% CI)	4.4 (0.0, 9.3)	4.5 (0.0, 13.2)
Percentage difference (Vutrisiran – Patisiran), (95% CI)	-0.134 (-10.113, 9.846)	
Odds ratio (Vutrisiran/Patisiran), (95% CI) [1]	0.969 (0.096, 9.823)	
Relative risk (Vutrisiran/Patisiran), (95% CI) [1]	0.971 (0.106, 8.861)	
P-value [2]	0.9789	
p-value of Treatment*Genotype [3]	0.6232	

N1 = Patients with missing postbaseline values due to COVID-19 or after initiation of local standard treatment for hATTR amyloidosis were included in analysis.
[1] Based on unstratified analysis.
In estimation of the odds ratio and relative risk, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the percentage difference or p-value.
[2] p-value based on the Wald test testing whether the relative risk equals to 1.
[3] p-value from a logistic regression with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Binary Subgroup Analysis
mITT Population

Month 9

Analysis Visit Statistics	Vutrisiran (HELIOS-A) (N=122)	Patisiran (HELIOS-A) (N=42)
FAP Stage		
I		
Patients included in analysis, N1	84	31
Improved, n(%)	0	0
No Change, n(%)	58 (69.0)	26 (83.9)
Worsened, n(%)	6 (7.1)	0
Missing, n(%)	20 (23.8)	5 (16.1)
Improved, (95% CI)	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)
Percentage difference (Vutrisiran – Patisiran), (95% CI)	- (-,-)	
Odds ratio (Vutrisiran/Patisiran), (95% CI) [1]	0.373 (0.007, 19.191)	
Relative risk (Vutrisiran/Patisiran), (95% CI) [1]	0.376 (0.008, 18.576)	
P-value [2]	0.6234	

N1 = Patients with missing postbaseline values due to COVID-19 or after initiation of local standard treatment for hATTR amyloidosis were included in analysis.
[1] Based on unstratified analysis.
In estimation of the odds ratio and relative risk, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the percentage difference or p-value.
[2] p-value based on the Wald test testing whether the relative risk equals to 1.
[3] p-value from a logistic regression with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Table 8.2
Familial Amyloidotic Polyneuropathy (FAP) Stage: Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A)
Binary Subgroup Analysis
mITT Population

Month 9

Analysis Visit Statistics	Vutrisiran (HELIOS-A) (N=122)	Patisiran (HELIOS-A) (N=42)
II&III		
Patients included in analysis, N1	38	11
Improved, n(%)	4 (10.5)	2 (18.2)
No Change, n(%)	26 (68.4)	6 (54.5)
Worsened, n(%)	0	0
Missing, n(%)	8 (21.1)	3 (27.3)
Improved, (95% CI)	10.5 (0.8, 20.3)	18.2 (0.0, 41.0)
Percentage difference (Vutrisiran – Patisiran), (95% CI)	-7.656 (-32.449, 17.138)	
Odds ratio (Vutrisiran/Patisiran), (95% CI) [1]	0.529 (0.083, 3.366)	
Relative risk (Vutrisiran/Patisiran), (95% CI) [1]	0.579 (0.122, 2.753)	
P-value [2]	0.4920	
p-value of Treatment*FAP Stage [3]	0.8981	

N1 = Patients with missing postbaseline values due to COVID-19 or after initiation of local standard treatment for hATTR amyloidosis were included in analysis.
[1] Based on unstratified analysis.
In estimation of the odds ratio and relative risk, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the percentage difference or p-value.
[2] p-value based on the Wald test testing whether the relative risk equals to 1.
[3] p-value from a logistic regression with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

Alnylam Pharmaceuticals Inc.
ALN-TTRSC02-002

Table 8.2
Familial Amyloidotic Polyneuropathy (FAP) Stage: Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A)
Binary Subgroup Analysis
mITT Population

Month 18

Analysis Visit Statistics	Vutrisiran (HELIOS-A) (N=122)	Patisiran (HELIOS-A) (N=42)
FAP Stage		
I		
Patients included in analysis, N1	84	31
Improved, n(%)	1 (1.2)	0
No Change, n(%)	73 (86.9)	29 (93.5)
Worsened, n(%)	7 (8.3)	1 (3.2)
Missing, n(%)	3 (3.6)	1 (3.2)
Improved, (95% CI)	1.2 (0.0, 3.5)	0.0 (0.0, 0.0)
Percentage difference (Vutrisiran – Patisiran), (95% CI)	1.190 (-1.129, 3.510)	
Odds ratio (Vutrisiran/Patisiran), (95% CI) [1]	1.132 (0.045, 28.517)	
Relative risk (Vutrisiran/Patisiran), (95% CI) [1]	1.129 (0.047, 27.015)	
P-value [2]	0.9401	

N1 = Patients with missing postbaseline values due to COVID-19 or after initiation of local standard treatment for hATTR amyloidosis were included in analysis.
[1] Based on unstratified analysis.
In estimation of the odds ratio and relative risk, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the percentage difference or p-value.
[2] p-value based on the Wald test testing whether the relative risk equals to 1.
[3] p-value from a logistic regression with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

Alnylam Pharmaceuticals Inc.
ALN-TTRSC02-002

Table 8.2
Familial Amyloidotic Polyneuropathy (FAP) Stage: Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A)
Binary Subgroup Analysis
mITT Population

Month 18

Analysis Visit Statistics	Vutrisiran (HELIOS-A) (N=122)	Patisiran (HELIOS-A) (N=42)
II&III		
Patients included in analysis, N1	38	11
Improved, n(%)	4 (10.5)	1 (9.1)
No Change, n(%)	28 (73.7)	7 (63.6)
Worsened, n(%)	2 (5.3)	0
Missing, n(%)	4 (10.5)	3 (27.3)
Improved, (95% CI)	10.5 (0.8, 20.3)	9.1 (0.0, 26.1)
Percentage difference (Vutrisiran – Patisiran), (95% CI)	1.435 (-18.156, 21.027)	
Odds ratio (Vutrisiran/Patisiran), (95% CI) [1]	1.176 (0.118, 11.757)	
Relative risk (Vutrisiran/Patisiran), (95% CI) [1]	1.158 (0.144, 9.324)	
P-value [2]	0.8904	
p-value of Treatment*FAP Stage [3]	0.9131	

N1 = Patients with missing postbaseline values due to COVID-19 or after initiation of local standard treatment for hATTR amyloidosis were included in analysis.
[1] Based on unstratified analysis.
In estimation of the odds ratio and relative risk, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the percentage difference or p-value.
[2] p-value based on the Wald test testing whether the relative risk equals to 1.
[3] p-value from a logistic regression with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

Alnylam Pharmaceuticals Inc.
ALN-TTRSC02-002

Table 8.2
Familial Amyloidotic Polyneuropathy (FAP) Stage: Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A)
Binary Subgroup Analysis
mITT Population

Month 9

Analysis Visit Statistics	Vutrisiran (HELIOS-A) (N=122)	Patisiran (HELIOS-A) (N=42)
Cardiac Subpopulation		
Yes		
Patients included in analysis, N1	40	14
Improved, n(%)	2 (5.0)	1 (7.1)
No Change, n(%)	29 (72.5)	12 (85.7)
Worsened, n(%)	2 (5.0)	0
Missing, n(%)	7 (17.5)	1 (7.1)
Improved, (95% CI)	5.0 (0.0, 11.8)	7.1 (0.0, 20.6)
Percentage difference (Vutrisiran – Patisiran), (95% CI)	-2.143 (-17.230, 12.944)	
Odds ratio (Vutrisiran/Patisiran), (95% CI) [1]	0.684 (0.057, 8.184)	
Relative risk (Vutrisiran/Patisiran), (95% CI) [1]	0.700 (0.069, 7.137)	
P-value [2]	0.7634	

N1 = Patients with missing postbaseline values due to COVID-19 or after initiation of local standard treatment for hATTR amyloidosis were included in analysis.
[1] Based on unstratified analysis.
In estimation of the odds ratio and relative risk, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the percentage difference or p-value.
[2] p-value based on the Wald test testing whether the relative risk equals to 1.
[3] p-value from a logistic regression with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

Alnylam Pharmaceuticals Inc.
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Table 8.2
Familial Amyloidotic Polyneuropathy (FAP) Stage: Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A)
Binary Subgroup Analysis
mITT Population

Month 9

Analysis Visit Statistics	Vutrisiran (HELIOS-A) (N=122)	Patisiran (HELIOS-A) (N=42)
No		
Patients included in analysis, N1	82	28
Improved, n(%)	2 (2.4)	1 (3.6)
No Change, n(%)	55 (67.1)	20 (71.4)
Worsened, n(%)	4 (4.9)	0
Missing, n(%)	21 (25.6)	7 (25.0)
Improved, (95% CI)	2.4 (0.0, 5.8)	3.6 (0.0, 10.4)
Percentage difference (Vutrisiran – Patisiran), (95% CI)	-1.132 (-8.774, 6.509)	
Odds ratio (Vutrisiran/Patisiran), (95% CI) [1]	0.675 (0.059, 7.743)	
Relative risk (Vutrisiran/Patisiran), (95% CI) [1]	0.683 (0.064, 7.246)	
P-value [2]	0.7516	
p-value of Treatment*Cardiac Subpopulation [3]	0.9866	

N1 = Patients with missing postbaseline values due to COVID-19 or after initiation of local standard treatment for hATTR amyloidosis were included in analysis.
[1] Based on unstratified analysis.
In estimation of the odds ratio and relative risk, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the percentage difference or p-value.
[2] p-value based on the Wald test testing whether the relative risk equals to 1.
[3] p-value from a logistic regression with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

Alnylam Pharmaceuticals Inc.
ALN-TTRSC02-002

Table 8.2
Familial Amyloidotic Polyneuropathy (FAP) Stage: Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A)
Binary Subgroup Analysis
mITT Population

Month 18

Analysis Visit Statistics	Vutrisiran (HELIOS-A) (N=122)	Patisiran (HELIOS-A) (N=42)
Cardiac Subpopulation		
Yes		
Patients included in analysis, N1	40	14
Improved, n(%)	3 (7.5)	1 (7.1)
No Change, n(%)	30 (75.0)	12 (85.7)
Worsened, n(%)	4 (10.0)	0
Missing, n(%)	3 (7.5)	1 (7.1)
Improved, (95% CI)	7.5 (0.0, 15.7)	7.1 (0.0, 20.6)
Percentage difference (Vutrisiran – Patisiran), (95% CI)	0.357 (-15.411, 16.125)	
Odds ratio (Vutrisiran/Patisiran), (95% CI) [1]	1.054 (0.101, 11.049)	
Relative risk (Vutrisiran/Patisiran), (95% CI) [1]	1.050 (0.119, 9.287)	
P-value [2]	0.9650	

N1 = Patients with missing postbaseline values due to COVID-19 or after initiation of local standard treatment for hATTR amyloidosis were included in analysis.
[1] Based on unstratified analysis.
In estimation of the odds ratio and relative risk, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the percentage difference or p-value.
[2] p-value based on the Wald test testing whether the relative risk equals to 1.
[3] p-value from a logistic regression with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

Alnylam Pharmaceuticals Inc.
ALN-TTRSC02-002

Table 8.2
Familial Amyloidotic Polyneuropathy (FAP) Stage: Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A)
Binary Subgroup Analysis
mITT Population

Month 18

Analysis Visit Statistics	Vutrisiran (HELIOS-A) (N=122)	Patisiran (HELIOS-A) (N=42)
No		
Patients included in analysis, N1	82	28
Improved, n(%)	2 (2.4)	0
No Change, n(%)	71 (86.6)	24 (85.7)
Worsened, n(%)	5 (6.1)	1 (3.6)
Missing, n(%)	4 (4.9)	3 (10.7)
Improved, (95% CI)	2.4 (0.0, 5.8)	0.0 (0.0, 0.0)
Percentage difference (Vutrisiran – Patisiran), (95% CI)	2.439 (-0.900, 5.778)	
Odds ratio (Vutrisiran/Patisiran), (95% CI) [1]	1.770 (0.082, 37.991)	
Relative risk (Vutrisiran/Patisiran), (95% CI) [1]	1.747 (0.086, 35.328)	
P-value [2]	0.7161	
p-value of Treatment*Cardiac Subpopulation [3]	0.6959	

N1 = Patients with missing postbaseline values due to COVID-19 or after initiation of local standard treatment for hATTR amyloidosis were included in analysis.
[1] Based on unstratified analysis.
In estimation of the odds ratio and relative risk, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the percentage difference or p-value.
[2] p-value based on the Wald test testing whether the relative risk equals to 1.
[3] p-value from a logistic regression with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Alnylam Pharmaceuticals Inc.
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Table 8.2
Familial Amyloidotic Polyneuropathy (FAP) Stage: Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A)
Binary Subgroup Analysis
mITT Population

Month 9

Analysis Visit Statistics	Vutrisiran (HELIOS-A) (N=122)	Patisiran (HELIOS-A) (N=42)
Weight (kg)		
<65 kg		
Patients included in analysis, N1	46	15
Improved, n(%)	2 (4.3)	1 (6.7)
No Change, n(%)	33 (71.7)	13 (86.7)
Worsened, n(%)	4 (8.7)	0
Missing, n(%)	7 (15.2)	1 (6.7)
Improved, (95% CI)	4.3 (0.0, 10.2)	6.7 (0.0, 19.3)
Percentage difference (Vutrisiran – Patisiran), (95% CI)	-2.319 (-16.250, 11.612)	
Odds ratio (Vutrisiran/Patisiran), (95% CI) [1]	0.636 (0.054, 7.558)	
Relative risk (Vutrisiran/Patisiran), (95% CI) [1]	0.652 (0.064, 6.694)	
P-value [2]	0.7190	

N1 = Patients with missing postbaseline values due to COVID-19 or after initiation of local standard treatment for hATTR amyloidosis were included in analysis.
[1] Based on unstratified analysis.
In estimation of the odds ratio and relative risk, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the percentage difference or p-value.
[2] p-value based on the Wald test testing whether the relative risk equals to 1.
[3] p-value from a logistic regression with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Alnylam Pharmaceuticals Inc.
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Table 8.2
Familial Amyloidotic Polyneuropathy (FAP) Stage: Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A)
Binary Subgroup Analysis
mITT Population

Month 9

Analysis Visit Statistics	Vutrisiran (HELIOS-A) (N=122)	Patisiran (HELIOS-A) (N=42)
≥65 kg		
Patients included in analysis, N1	76	27
Improved, n(%)	2 (2.6)	1 (3.7)
No Change, n(%)	51 (67.1)	19 (70.4)
Worsened, n(%)	2 (2.6)	0
Missing, n(%)	21 (27.6)	7 (25.9)
Improved, (95% CI)	2.6 (0.0, 6.2)	3.7 (0.0, 10.8)
Percentage difference (Vutrisiran – Patisiran), (95% CI)	-1.072 (-9.053, 6.909)	
Odds ratio (Vutrisiran/Patisiran), (95% CI) [1]	0.703 (0.061, 8.076)	
Relative risk (Vutrisiran/Patisiran), (95% CI) [1]	0.711 (0.067, 7.525)	
P-value [2]	0.7765	
p-value of Treatment*Weight (kg) [3]	0.9545	

N1 = Patients with missing postbaseline values due to COVID-19 or after initiation of local standard treatment for hATTR amyloidosis were included in analysis.
[1] Based on unstratified analysis.
In estimation of the odds ratio and relative risk, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the percentage difference or p-value.
[2] p-value based on the Wald test testing whether the relative risk equals to 1.
[3] p-value from a logistic regression with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Alnylam Pharmaceuticals Inc.
ALN-TTRSC02-002

Table 8.2
Familial Amyloidotic Polyneuropathy (FAP) Stage: Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A)
Binary Subgroup Analysis
mITT Population

Month 18

Analysis Visit Statistics	Vutrisiran (HELIOS-A) (N=122)	Patisiran (HELIOS-A) (N=42)
Weight (kg)		
<65 kg		
Patients included in analysis, N1	46	15
Improved, n(%)	3 (6.5)	0
No Change, n(%)	34 (73.9)	15 (100.0)
Worsened, n(%)	5 (10.9)	0
Missing, n(%)	4 (8.7)	0
Improved, (95% CI)	6.5 (0.0, 13.7)	0.0 (0.0, 0.0)
Percentage difference (Vutrisiran – Patisiran), (95% CI)	6.522 (-0.613, 13.657)	
Odds ratio (Vutrisiran/Patisiran), (95% CI) [1]	2.494 (0.122, 51.079)	
Relative risk (Vutrisiran/Patisiran), (95% CI) [1]	2.383 (0.130, 43.673)	
P-value [2]	0.5584	

N1 = Patients with missing postbaseline values due to COVID-19 or after initiation of local standard treatment for hATTR amyloidosis were included in analysis.
[1] Based on unstratified analysis.
In estimation of the odds ratio and relative risk, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the percentage difference or p-value.
[2] p-value based on the Wald test testing whether the relative risk equals to 1.
[3] p-value from a logistic regression with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

Alnylam Pharmaceuticals Inc.
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Table 8.2
Familial Amyloidotic Polyneuropathy (FAP) Stage: Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A)
Binary Subgroup Analysis
mITT Population

Month 18

Analysis Visit Statistics	Vutrisiran (HELIOS-A) (N=122)	Patisiran (HELIOS-A) (N=42)
≥65 kg		
Patients included in analysis, N1	76	27
Improved, n(%)	2 (2.6)	1 (3.7)
No Change, n(%)	67 (88.2)	21 (77.8)
Worsened, n(%)	4 (5.3)	1 (3.7)
Missing, n(%)	3 (3.9)	4 (14.8)
Improved, (95% CI)	2.6 (0.0, 6.2)	3.7 (0.0, 10.8)
Percentage difference (Vutrisiran – Patisiran), (95% CI)	-1.072 (-9.053, 6.909)	
Odds ratio (Vutrisiran/Patisiran), (95% CI) [1]	0.703 (0.061, 8.076)	
Relative risk (Vutrisiran/Patisiran), (95% CI) [1]	0.711 (0.067, 7.525)	
P-value [2]	0.7765	
p-value of Treatment*Weight (kg) [3]	0.4531	

N1 = Patients with missing postbaseline values due to COVID-19 or after initiation of local standard treatment for hATTR amyloidosis were included in analysis.
[1] Based on unstratified analysis.
In estimation of the odds ratio and relative risk, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the percentage difference or p-value.
[2] p-value based on the Wald test testing whether the relative risk equals to 1.
[3] p-value from a logistic regression with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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PND-Wert

Alnylam Pharmaceuticals Inc.
ALN-TTRSC02-002

Table 9.2
Polyneuropathy Disability (PND) Score: Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A)
Binary Subgroup Analysis
mITT Population

Month 9

Analysis Visit Statistics	Vutrisiran (HELIOS-A) (N=122)	Patisiran (HELIOS-A) (N=42)
Age (years)		
<65		
Patients included in analysis, N1	76	31
Improved, n(%)	4 (5.3)	0
No Change, n(%)	47 (61.8)	22 (71.0)
Worsened, n(%)	8 (10.5)	4 (12.9)
Missing, n(%)	17 (22.4)	5 (16.1)
Improved, (95% CI)	5.3 (0.2, 10.3)	0.0 (0.0, 0.0)
Percentage difference (Vutrisiran – Patisiran), (95% CI)	5.263 (0.243, 10.283)	
Odds ratio (Vutrisiran/Patisiran), (95% CI) [1]	3.910 (0.204, 74.825)	
Relative risk (Vutrisiran/Patisiran), (95% CI) [1]	3.740 (0.207, 67.469)	
P-value [2]	0.3714	

N1 = Patients with missing postbaseline values due to COVID-19 or after initiation of local standard treatment for hATTR amyloidosis were included in analysis.
[1] Based on unstratified analysis.
In estimation of the odds ratio and relative risk, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the percentage difference or p-value.
[2] p-value based on the Wald test testing whether the relative risk equals to 1.
[3] p-value from a logistic regression with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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ALN-TTRSC02-002

Table 9.2
Polyneuropathy Disability (PND) Score: Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A)
Binary Subgroup Analysis
mITT Population

Month 9

Analysis Visit Statistics	Vutrisiran (HELIOS-A) (N=122)	Patisiran (HELIOS-A) (N=42)
≥65		
Patients included in analysis, N1	46	11
Improved, n(%)	4 (8.7)	0
No Change, n(%)	25 (54.3)	7 (63.6)
Worsened, n(%)	6 (13.0)	1 (9.1)
Missing, n(%)	11 (23.9)	3 (27.3)
Improved, (95% CI)	8.7 (0.6, 16.8)	0.0 (0.0, 0.0)
Percentage difference (Vutrisiran – Patisiran), (95% CI)	8.696 (0.553, 16.838)	
Odds ratio (Vutrisiran/Patisiran), (95% CI) [1]	2.435 (0.122, 48.597)	
Relative risk (Vutrisiran/Patisiran), (95% CI) [1]	2.298 (0.133, 39.810)	
P-value [2]	0.5675	
p-value of Treatment*Age [3]	0.8300	

N1 = Patients with missing postbaseline values due to COVID-19 or after initiation of local standard treatment for hATTR amyloidosis were included in analysis.
[1] Based on unstratified analysis.
In estimation of the odds ratio and relative risk, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the percentage difference or p-value.
[2] p-value based on the Wald test testing whether the relative risk equals to 1.
[3] p-value from a logistic regression with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Table 9.2
Polyneuropathy Disability (PND) Score: Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A)
Binary Subgroup Analysis
mITT Population

Month 18

Analysis Visit Statistics	Vutrisiran (HELIOS-A) (N=122)	Patisiran (HELIOS-A) (N=42)
Age (years)		
<65		
Patients included in analysis, N1	76	31
Improved, n(%)	7 (9.2)	1 (3.2)
No Change, n(%)	56 (73.7)	23 (74.2)
Worsened, n(%)	11 (14.5)	5 (16.1)
Missing, n(%)	2 (2.6)	2 (6.5)
Improved, (95% CI)	9.2 (2.7, 15.7)	3.2 (0.0, 9.4)
Percentage difference (Vutrisiran – Patisiran), (95% CI)	5.985 (-3.013, 14.982)	
Odds ratio (Vutrisiran/Patisiran), (95% CI) [1]	3.043 (0.359, 25.834)	
Relative risk (Vutrisiran/Patisiran), (95% CI) [1]	2.855 (0.366, 22.251)	
P-value [2]	0.3166	

N1 = Patients with missing postbaseline values due to COVID-19 or after initiation of local standard treatment for hATTR amyloidosis were included in analysis.
[1] Based on unstratified analysis.
In estimation of the odds ratio and relative risk, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the percentage difference or p-value.
[2] p-value based on the Wald test testing whether the relative risk equals to 1.
[3] p-value from a logistic regression with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Table 9.2
Polyneuropathy Disability (PND) Score: Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A)
Binary Subgroup Analysis
mITT Population

Month 18

Analysis Visit Statistics	Vutrisiran (HELIOS-A) (N=122)	Patisiran (HELIOS-A) (N=42)
≥65		
Patients included in analysis, N1	46	11
Improved, n(%)	6 (13.0)	0
No Change, n(%)	26 (56.5)	7 (63.6)
Worsened, n(%)	9 (19.6)	2 (18.2)
Missing, n(%)	5 (10.9)	2 (18.2)
Improved, (95% CI)	13.0 (3.3, 22.8)	0.0 (0.0, 0.0)
Percentage difference (Vutrisiran – Patisiran), (95% CI)	13.043 (3.311, 22.776)	
Odds ratio (Vutrisiran/Patisiran), (95% CI) [1]	3.691 (0.193, 70.531)	
Relative risk (Vutrisiran/Patisiran), (95% CI) [1]	3.319 (0.201, 54.895)	
P-value [2]	0.4020	
p-value of Treatment*Age [3]	0.7757	

N1 = Patients with missing postbaseline values due to COVID-19 or after initiation of local standard treatment for hATTR amyloidosis were included in analysis.
[1] Based on unstratified analysis.
In estimation of the odds ratio and relative risk, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the percentage difference or p-value.
[2] p-value based on the Wald test testing whether the relative risk equals to 1.
[3] p-value from a logistic regression with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Table 9.2
Polyneuropathy Disability (PND) Score: Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A)
Binary Subgroup Analysis
mITT Population

Month 9

Analysis Visit Statistics	Vutrisiran (HELIOS-A) (N=122)	Patisiran (HELIOS-A) (N=42)
Sex		
Male		
Patients included in analysis, N1	79	27
Improved, n(%)	4 (5.1)	0
No Change, n(%)	46 (58.2)	20 (74.1)
Worsened, n(%)	11 (13.9)	2 (7.4)
Missing, n(%)	18 (22.8)	5 (18.5)
Improved, (95% CI)	5.1 (0.2, 9.9)	0.0 (0.0, 0.0)
Percentage difference (Vutrisiran – Patisiran), (95% CI)	5.063 (0.229, 9.898)	
Odds ratio (Vutrisiran/Patisiran), (95% CI) [1]	3.278 (0.171, 62.894)	
Relative risk (Vutrisiran/Patisiran), (95% CI) [1]	3.150 (0.175, 56.672)	
P-value [2]	0.4365	

N1 = Patients with missing postbaseline values due to COVID-19 or after initiation of local standard treatment for hATTR amyloidosis were included in analysis.
[1] Based on unstratified analysis.
In estimation of the odds ratio and relative risk, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the percentage difference or p-value.
[2] p-value based on the Wald test testing whether the relative risk equals to 1.
[3] p-value from a logistic regression with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Table 9.2
Polyneuropathy Disability (PND) Score: Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A)
Binary Subgroup Analysis
mITT Population

Month 9

Analysis Visit Statistics	Vutrisiran (HELIOS-A) (N=122)	Patisiran (HELIOS-A) (N=42)
Female		
Patients included in analysis, N1	43	15
Improved, n(%)	4 (9.3)	0
No Change, n(%)	26 (60.5)	9 (60.0)
Worsened, n(%)	3 (7.0)	3 (20.0)
Missing, n(%)	10 (23.3)	3 (20.0)
Improved, (95% CI)	9.3 (0.6, 18.0)	0.0 (0.0, 0.0)
Percentage difference (Vutrisiran – Patisiran), (95% CI)	9.302 (0.621, 17.984)	
Odds ratio (Vutrisiran/Patisiran), (95% CI) [1]	3.532 (0.179, 69.545)	
Relative risk (Vutrisiran/Patisiran), (95% CI) [1]	3.273 (0.186, 57.443)	
P-value [2]	0.4173	
p-value of Treatment*Sex [3]	0.9729	

N1 = Patients with missing postbaseline values due to COVID-19 or after initiation of local standard treatment for hATTR amyloidosis were included in analysis.
[1] Based on unstratified analysis.
In estimation of the odds ratio and relative risk, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the percentage difference or p-value.
[2] p-value based on the Wald test testing whether the relative risk equals to 1.
[3] p-value from a logistic regression with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Table 9.2
Polyneuropathy Disability (PND) Score: Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A)
Binary Subgroup Analysis
mITT Population

Month 18

Analysis Visit Statistics	Vutrisiran (HELIOS-A) (N=122)	Patisiran (HELIOS-A) (N=42)
Sex		
Male		
Patients included in analysis, N1	79	27
Improved, n(%)	6 (7.6)	0
No Change, n(%)	52 (65.8)	19 (70.4)
Worsened, n(%)	16 (20.3)	4 (14.8)
Missing, n(%)	5 (6.3)	4 (14.8)
Improved, (95% CI)	7.6 (1.8, 13.4)	0.0 (0.0, 0.0)
Percentage difference (Vutrisiran – Patisiran), (95% CI)	7.595 (1.753, 13.437)	
Odds ratio (Vutrisiran/Patisiran), (95% CI) [1]	4.864 (0.265, 89.252)	
Relative risk (Vutrisiran/Patisiran), (95% CI) [1]	4.550 (0.265, 78.194)	
P-value [2]	0.2964	

N1 = Patients with missing postbaseline values due to COVID-19 or after initiation of local standard treatment for hATTR amyloidosis were included in analysis.
[1] Based on unstratified analysis.
In estimation of the odds ratio and relative risk, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the percentage difference or p-value.
[2] p-value based on the Wald test testing whether the relative risk equals to 1.
[3] p-value from a logistic regression with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Table 9.2
Polyneuropathy Disability (PND) Score: Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A)
Binary Subgroup Analysis
mITT Population

Month 18

Analysis Visit Statistics	Vutrisiran (HELIOS-A) (N=122)	Patisiran (HELIOS-A) (N=42)
Female		
Patients included in analysis, N1	43	15
Improved, n(%)	7 (16.3)	1 (6.7)
No Change, n(%)	30 (69.8)	11 (73.3)
Worsened, n(%)	4 (9.3)	3 (20.0)
Missing, n(%)	2 (4.7)	0
Improved, (95% CI)	16.3 (5.2, 27.3)	6.7 (0.0, 19.3)
Percentage difference (Vutrisiran – Patisiran), (95% CI)	9.612 (-7.154, 26.379)	
Odds ratio (Vutrisiran/Patisiran), (95% CI) [1]	2.722 (0.306, 24.186)	
Relative risk (Vutrisiran/Patisiran), (95% CI) [1]	2.442 (0.327, 18.246)	
P-value [2]	0.3843	
p-value of Treatment*Sex [3]	0.6182	

N1 = Patients with missing postbaseline values due to COVID-19 or after initiation of local standard treatment for hATTR amyloidosis were included in analysis.
[1] Based on unstratified analysis.
In estimation of the odds ratio and relative risk, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the percentage difference or p-value.
[2] p-value based on the Wald test testing whether the relative risk equals to 1.
[3] p-value from a logistic regression with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Table 9.2
Polyneuropathy Disability (PND) Score: Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A)
Binary Subgroup Analysis
mITT Population

Month 9

Analysis Visit Statistics	Vutrisiran (HELIOS-A) (N=122)	Patisiran (HELIOS-A) (N=42)
Race		
White		
Patients included in analysis, N1	86	29
Improved, n(%)	5 (5.8)	0
No Change, n(%)	54 (62.8)	23 (79.3)
Worsened, n(%)	8 (9.3)	2 (6.9)
Missing, n(%)	19 (22.1)	4 (13.8)
Improved, (95% CI)	5.8 (0.9, 10.8)	0.0 (0.0, 0.0)
Percentage difference (Vutrisiran – Patisiran), (95% CI)	5.814 (0.868, 10.760)	
Odds ratio (Vutrisiran/Patisiran), (95% CI) [1]	3.982 (0.214, 74.233)	
Relative risk (Vutrisiran/Patisiran), (95% CI) [1]	3.793 (0.216, 66.576)	
P-value [2]	0.3618	

N1 = Patients with missing postbaseline values due to COVID-19 or after initiation of local standard treatment for hATTR amyloidosis were included in analysis.
[1] Based on unstratified analysis.
In estimation of the odds ratio and relative risk, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the percentage difference or p-value.
[2] p-value based on the Wald test testing whether the relative risk equals to 1.
[3] p-value from a logistic regression with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Table 9.2
Polyneuropathy Disability (PND) Score: Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A)
Binary Subgroup Analysis
mITT Population

Month 9

Analysis Visit Statistics	Vutrisiran (HELIOS-A) (N=122)	Patisiran (HELIOS-A) (N=42)
All Other Races		
Patients included in analysis, N1	36	13
Improved, n(%)	3 (8.3)	0
No Change, n(%)	18 (50.0)	6 (46.2)
Worsened, n(%)	6 (16.7)	3 (23.1)
Missing, n(%)	9 (25.0)	4 (30.8)
Improved, (95% CI)	8.3 (0.0, 17.4)	0.0 (0.0, 0.0)
Percentage difference (Vutrisiran – Patisiran), (95% CI)	8.333 (-0.695, 17.362)	
Odds ratio (Vutrisiran/Patisiran), (95% CI) [1]	2.821 (0.136, 58.373)	
Relative risk (Vutrisiran/Patisiran), (95% CI) [1]	2.649 (0.146, 48.073)	
P-value [2]	0.5101	
p-value of Treatment*Race [3]	0.8757	

N1 = Patients with missing postbaseline values due to COVID-19 or after initiation of local standard treatment for hATTR amyloidosis were included in analysis.
[1] Based on unstratified analysis.
In estimation of the odds ratio and relative risk, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the percentage difference or p-value.
[2] p-value based on the Wald test testing whether the relative risk equals to 1.
[3] p-value from a logistic regression with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Table 9.2
Polyneuropathy Disability (PND) Score: Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A)
Binary Subgroup Analysis
mITT Population

Month 18

Analysis Visit Statistics	Vutrisiran (HELIOS-A) (N=122)	Patisiran (HELIOS-A) (N=42)
Race		
White		
Patients included in analysis, N1	86	29
Improved, n(%)	6 (7.0)	1 (3.4)
No Change, n(%)	65 (75.6)	21 (72.4)
Worsened, n(%)	11 (12.8)	5 (17.2)
Missing, n(%)	4 (4.7)	2 (6.9)
Improved, (95% CI)	7.0 (1.6, 12.4)	3.4 (0.0, 10.1)
Percentage difference (Vutrisiran – Patisiran), (95% CI)	3.528 (-5.021, 12.078)	
Odds ratio (Vutrisiran/Patisiran), (95% CI) [1]	2.100 (0.242, 18.215)	
Relative risk (Vutrisiran/Patisiran), (95% CI) [1]	2.023 (0.254, 16.110)	
P-value [2]	0.5056	

N1 = Patients with missing postbaseline values due to COVID-19 or after initiation of local standard treatment for hATTR amyloidosis were included in analysis.
[1] Based on unstratified analysis.
In estimation of the odds ratio and relative risk, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the percentage difference or p-value.
[2] p-value based on the Wald test testing whether the relative risk equals to 1.
[3] p-value from a logistic regression with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Table 9.2
Polyneuropathy Disability (PND) Score: Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A)
Binary Subgroup Analysis
mITT Population

Month 18

Analysis Visit Statistics	Vutrisiran (HELIOS-A) (N=122)	Patisiran (HELIOS-A) (N=42)
All Other Races		
Patients included in analysis, N1	36	13
Improved, n(%)	7 (19.4)	0
No Change, n(%)	17 (47.2)	9 (69.2)
Worsened, n(%)	9 (25.0)	2 (15.4)
Missing, n(%)	3 (8.3)	2 (15.4)
Improved, (95% CI)	19.4 (6.5, 32.4)	0.0 (0.0, 0.0)
Percentage difference (Vutrisiran – Patisiran), (95% CI)	19.444 (6.516, 32.373)	
Odds ratio (Vutrisiran/Patisiran), (95% CI) [1]	6.864 (0.365, 129.103)	
Relative risk (Vutrisiran/Patisiran), (95% CI) [1]	5.676 (0.347, 92.950)	
P-value [2]	0.2236	
p-value of Treatment*Race [3]	0.4095	

N1 = Patients with missing postbaseline values due to COVID-19 or after initiation of local standard treatment for hATTR amyloidosis were included in analysis.
[1] Based on unstratified analysis.
In estimation of the odds ratio and relative risk, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the percentage difference or p-value.
[2] p-value based on the Wald test testing whether the relative risk equals to 1.
[3] p-value from a logistic regression with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Table 9.2
Polyneuropathy Disability (PND) Score: Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A)
Binary Subgroup Analysis
mITT Population

Month 9

Analysis Visit Statistics	Vutrisiran (HELIOS-A) (N=122)	Patisiran (HELIOS-A) (N=42)
Region		
North America		
Patients included in analysis, N1	27	8
Improved, n(%)	1 (3.7)	0
No Change, n(%)	13 (48.1)	4 (50.0)
Worsened, n(%)	2 (7.4)	1 (12.5)
Missing, n(%)	11 (40.7)	3 (37.5)
Improved, (95% CI)	3.7 (0.0, 10.8)	0.0 (0.0, 0.0)
Percentage difference (Vutrisiran – Patisiran), (95% CI)	3.704 (-3.420, 10.827)	
Odds ratio (Vutrisiran/Patisiran), (95% CI) [1]	0.962 (0.036, 25.895)	
Relative risk (Vutrisiran/Patisiran), (95% CI) [1]	0.964 (0.043, 21.647)	
P-value [2]	0.9817	

N1 = Patients with missing postbaseline values due to COVID-19 or after initiation of local standard treatment for hATTR amyloidosis were included in analysis.
[1] Based on unstratified analysis.
In estimation of the odds ratio and relative risk, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the percentage difference or p-value.
[2] p-value based on the Wald test testing whether the relative risk equals to 1.
[3] p-value from a logistic regression with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Binary Subgroup Analysis
mITT Population

Month 9

Analysis Visit Statistics	Vutrisiran (HELIOS-A) (N=122)	Patisiran (HELIOS-A) (N=42)
Western Europe		
Patients included in analysis, N1	42	20
Improved, n(%)	4 (9.5)	0
No Change, n(%)	29 (69.0)	15 (75.0)
Worsened, n(%)	6 (14.3)	1 (5.0)
Missing, n(%)	3 (7.1)	4 (20.0)
Improved, (95% CI)	9.5 (0.6, 18.4)	0.0 (0.0, 0.0)
Percentage difference (Vutrisiran – Patisiran), (95% CI)	9.524 (0.646, 18.401)	
Odds ratio (Vutrisiran/Patisiran), (95% CI) [1]	4.792 (0.246, 93.454)	
Relative risk (Vutrisiran/Patisiran), (95% CI) [1]	4.395 (0.248, 77.892)	
P-value [2]	0.3128	

N1 = Patients with missing postbaseline values due to COVID-19 or after initiation of local standard treatment for hATTR amyloidosis were included in analysis.
[1] Based on unstratified analysis.
In estimation of the odds ratio and relative risk, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the percentage difference or p-value.
[2] p-value based on the Wald test testing whether the relative risk equals to 1.
[3] p-value from a logistic regression with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Table 9.2
Polyneuropathy Disability (PND) Score: Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A)
Binary Subgroup Analysis
mITT Population

Month 9

Analysis Visit Statistics	Vutrisiran (HELIOS-A) (N=122)	Patisiran (HELIOS-A) (N=42)
Rest of World		
Patients included in analysis, N1	53	14
Improved, n(%)	3 (5.7)	0
No Change, n(%)	30 (56.6)	10 (71.4)
Worsened, n(%)	6 (11.3)	3 (21.4)
Missing, n(%)	14 (26.4)	1 (7.1)
Improved, (95% CI)	5.7 (0.0, 11.9)	0.0 (0.0, 0.0)
Percentage difference (Vutrisiran – Patisiran), (95% CI)	5.660 (-0.561, 11.882)	
Odds ratio (Vutrisiran/Patisiran), (95% CI) [1]	2.010 (0.098, 41.193)	
Relative risk (Vutrisiran/Patisiran), (95% CI) [1]	1.944 (0.106, 35.603)	
P-value [2]	0.6540	
p-value of Treatment*Region [3]	0.7888	

N1 = Patients with missing postbaseline values due to COVID-19 or after initiation of local standard treatment for hATTR amyloidosis were included in analysis.
[1] Based on unstratified analysis.
In estimation of the odds ratio and relative risk, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the percentage difference or p-value.
[2] p-value based on the Wald test testing whether the relative risk equals to 1.
[3] p-value from a logistic regression with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Table 9.2
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Binary Subgroup Analysis
mITT Population

Month 18

Analysis Visit Statistics	Vutrisiran (HELIOS-A) (N=122)	Patisiran (HELIOS-A) (N=42)
Region		
North America		
Patients included in analysis, N1	27	8
Improved, n(%)	2 (7.4)	0
No Change, n(%)	18 (66.7)	4 (50.0)
Worsened, n(%)	5 (18.5)	3 (37.5)
Missing, n(%)	2 (7.4)	1 (12.5)
Improved, (95% CI)	7.4 (0.0, 17.3)	0.0 (0.0, 0.0)
Percentage difference (Vutrisiran – Patisiran), (95% CI)	7.407 (-2.471, 17.286)	
Odds ratio (Vutrisiran/Patisiran), (95% CI) [1]	1.667 (0.073, 38.277)	
Relative risk (Vutrisiran/Patisiran), (95% CI) [1]	1.607 (0.085, 30.462)	
P-value [2]	0.7519	

N1 = Patients with missing postbaseline values due to COVID-19 or after initiation of local standard treatment for hATTR amyloidosis were included in analysis.
[1] Based on unstratified analysis.
In estimation of the odds ratio and relative risk, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the percentage difference or p-value.
[2] p-value based on the Wald test testing whether the relative risk equals to 1.
[3] p-value from a logistic regression with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Polyneuropathy Disability (PND) Score: Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A)
Binary Subgroup Analysis
mITT Population

Month 18

Analysis Visit Statistics	Vutrisiran (HELIOS-A) (N=122)	Patisiran (HELIOS-A) (N=42)
Western Europe		
Patients included in analysis, N1	42	20
Improved, n(%)	3 (7.1)	0
No Change, n(%)	31 (73.8)	16 (80.0)
Worsened, n(%)	6 (14.3)	2 (10.0)
Missing, n(%)	2 (4.8)	2 (10.0)
Improved, (95% CI)	7.1 (0.0, 14.9)	0.0 (0.0, 0.0)
Percentage difference (Vutrisiran – Patisiran), (95% CI)	7.143 (-0.646, 14.932)	
Odds ratio (Vutrisiran/Patisiran), (95% CI) [1]	3.633 (0.179, 73.764)	
Relative risk (Vutrisiran/Patisiran), (95% CI) [1]	3.419 (0.185, 63.188)	
P-value [2]	0.4088	

N1 = Patients with missing postbaseline values due to COVID-19 or after initiation of local standard treatment for hATTR amyloidosis were included in analysis.
[1] Based on unstratified analysis.
In estimation of the odds ratio and relative risk, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the percentage difference or p-value.
[2] p-value based on the Wald test testing whether the relative risk equals to 1.
[3] p-value from a logistic regression with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Table 9.2
Polyneuropathy Disability (PND) Score: Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A)
Binary Subgroup Analysis
mITT Population

Month 18

Analysis Visit Statistics	Vutrisiran (HELIOS-A) (N=122)	Patisiran (HELIOS-A) (N=42)
Rest of World		
Patients included in analysis, N1	53	14
Improved, n(%)	8 (15.1)	1 (7.1)
No Change, n(%)	33 (62.3)	10 (71.4)
Worsened, n(%)	9 (17.0)	2 (14.3)
Missing, n(%)	3 (5.7)	1 (7.1)
Improved, (95% CI)	15.1 (5.5, 24.7)	7.1 (0.0, 20.6)
Percentage difference (Vutrisiran – Patisiran), (95% CI)	7.951 (-8.628, 24.531)	
Odds ratio (Vutrisiran/Patisiran), (95% CI) [1]	2.311 (0.264, 20.212)	
Relative risk (Vutrisiran/Patisiran), (95% CI) [1]	2.113 (0.288, 15.516)	
P-value [2]	0.4620	
p-value of Treatment*Region [3]	0.9102	

N1 = Patients with missing postbaseline values due to COVID-19 or after initiation of local standard treatment for hATTR amyloidosis were included in analysis.
[1] Based on unstratified analysis.
In estimation of the odds ratio and relative risk, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the percentage difference or p-value.
[2] p-value based on the Wald test testing whether the relative risk equals to 1.
[3] p-value from a logistic regression with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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ALN-TTRSC02-002

Table 9.2
Polyneuropathy Disability (PND) Score: Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A)
Binary Subgroup Analysis
mITT Population

Month 9

Analysis Visit Statistics	Vutrisiran (HELIOS-A) (N=122)	Patisiran (HELIOS-A) (N=42)
Baseline NIS		
<50		
Patients included in analysis, N1	78	27
Improved, n(%)	6 (7.7)	0
No Change, n(%)	46 (59.0)	18 (66.7)
Worsened, n(%)	6 (7.7)	3 (11.1)
Missing, n(%)	20 (25.6)	6 (22.2)
Improved, (95% CI)	7.7 (1.8, 13.6)	0.0 (0.0, 0.0)
Percentage difference (Vutrisiran – Patisiran), (95% CI)	7.692 (1.779, 13.606)	
Odds ratio (Vutrisiran/Patisiran), (95% CI) [1]	4.931 (0.269, 90.494)	
Relative risk (Vutrisiran/Patisiran), (95% CI) [1]	4.608 (0.268, 79.175)	
P-value [2]	0.2924	

N1 = Patients with missing postbaseline values due to COVID-19 or after initiation of local standard treatment for hATTR amyloidosis were included in analysis.
[1] Based on unstratified analysis.
In estimation of the odds ratio and relative risk, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the percentage difference or p-value.
[2] p-value based on the Wald test testing whether the relative risk equals to 1.
[3] p-value from a logistic regression with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Table 9.2
Polyneuropathy Disability (PND) Score: Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A)
Binary Subgroup Analysis
mITT Population

Month 9

Analysis Visit Statistics	Vutrisiran (HELIOS-A) (N=122)	Patisiran (HELIOS-A) (N=42)
≥50		
Patients included in analysis, N1	44	15
Improved, n(%)	2 (4.5)	0
No Change, n(%)	26 (59.1)	11 (73.3)
Worsened, n(%)	8 (18.2)	2 (13.3)
Missing, n(%)	8 (18.2)	2 (13.3)
Improved, (95% CI)	4.5 (0.0, 10.7)	0.0 (0.0, 0.0)
Percentage difference (Vutrisiran – Patisiran), (95% CI)	4.545 (-1.609, 10.700)	
Odds ratio (Vutrisiran/Patisiran), (95% CI) [1]	1.824 (0.083, 40.138)	
Relative risk (Vutrisiran/Patisiran), (95% CI) [1]	1.778 (0.090, 35.081)	
P-value [2]	0.7053	
p-value of Treatment*Baseline NIS [3]	0.6537	

N1 = Patients with missing postbaseline values due to COVID-19 or after initiation of local standard treatment for hATTR amyloidosis were included in analysis.
[1] Based on unstratified analysis.
In estimation of the odds ratio and relative risk, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the percentage difference or p-value.
[2] p-value based on the Wald test testing whether the relative risk equals to 1.
[3] p-value from a logistic regression with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Table 9.2
Polyneuropathy Disability (PND) Score: Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A)
Binary Subgroup Analysis
mITT Population

Month 18

Analysis Visit Statistics	Vutrisiran (HELIOS-A) (N=122)	Patisiran (HELIOS-A) (N=42)
Baseline NIS		
<50		
Patients included in analysis, N1	78	27
Improved, n(%)	10 (12.8)	1 (3.7)
No Change, n(%)	57 (73.1)	20 (74.1)
Worsened, n(%)	8 (10.3)	5 (18.5)
Missing, n(%)	3 (3.8)	1 (3.7)
Improved, (95% CI)	12.8 (5.4, 20.2)	3.7 (0.0, 10.8)
Percentage difference (Vutrisiran – Patisiran), (95% CI)	9.117 (-1.169, 19.402)	
Odds ratio (Vutrisiran/Patisiran), (95% CI) [1]	3.824 (0.466, 31.371)	
Relative risk (Vutrisiran/Patisiran), (95% CI) [1]	3.462 (0.465, 25.796)	
P-value [2]	0.2256	

N1 = Patients with missing postbaseline values due to COVID-19 or after initiation of local standard treatment for hATTR amyloidosis were included in analysis.
[1] Based on unstratified analysis.
In estimation of the odds ratio and relative risk, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the percentage difference or p-value.
[2] p-value based on the Wald test testing whether the relative risk equals to 1.
[3] p-value from a logistic regression with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Table 9.2
Polyneuropathy Disability (PND) Score: Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A)
Binary Subgroup Analysis
mITT Population

Month 18

Analysis Visit Statistics	Vutrisiran (HELIOS-A) (N=122)	Patisiran (HELIOS-A) (N=42)
≥50		
Patients included in analysis, N1	44	15
Improved, n(%)	3 (6.8)	0
No Change, n(%)	25 (56.8)	10 (66.7)
Worsened, n(%)	12 (27.3)	2 (13.3)
Missing, n(%)	4 (9.1)	3 (20.0)
Improved, (95% CI)	6.8 (0.0, 14.3)	0.0 (0.0, 0.0)
Percentage difference (Vutrisiran – Patisiran), (95% CI)	6.818 (-0.630, 14.266)	
Odds ratio (Vutrisiran/Patisiran), (95% CI) [1]	2.614 (0.128, 53.578)	
Relative risk (Vutrisiran/Patisiran), (95% CI) [1]	2.489 (0.136, 45.585)	
P-value [2]	0.5388	
p-value of Treatment*Baseline NIS [3]	0.9846	

N1 = Patients with missing postbaseline values due to COVID-19 or after initiation of local standard treatment for hATTR amyloidosis were included in analysis.
[1] Based on unstratified analysis.
In estimation of the odds ratio and relative risk, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the percentage difference or p-value.
[2] p-value based on the Wald test testing whether the relative risk equals to 1.
[3] p-value from a logistic regression with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Table 9.2
Polyneuropathy Disability (PND) Score: Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A)
Binary Subgroup Analysis
mITT Population

Month 9

Analysis Visit Statistics	Vutrisiran (HELIOS-A) (N=122)	Patisiran (HELIOS-A) (N=42)
Previous Tetramer Stabilizer Use		
Yes		
Patients included in analysis, N1	75	33
Improved, n(%)	6 (8.0)	0
No Change, n(%)	54 (72.0)	25 (75.8)
Worsened, n(%)	8 (10.7)	4 (12.1)
Missing, n(%)	7 (9.3)	4 (12.1)
Improved, (95% CI)	8.0 (1.9, 14.1)	0.0 (0.0, 0.0)
Percentage difference (Vutrisiran – Patisiran), (95% CI)	8.000 (1.860, 14.140)	
Odds ratio (Vutrisiran/Patisiran), (95% CI) [1]	6.266 (0.343, 114.549)	
Relative risk (Vutrisiran/Patisiran), (95% CI) [1]	5.816 (0.337, 100.328)	
P-value [2]	0.2256	

N1 = Patients with missing postbaseline values due to COVID-19 or after initiation of local standard treatment for hATTR amyloidosis were included in analysis.
[1] Based on unstratified analysis.
In estimation of the odds ratio and relative risk, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the percentage difference or p-value.
[2] p-value based on the Wald test testing whether the relative risk equals to 1.
[3] p-value from a logistic regression with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Table 9.2
Polyneuropathy Disability (PND) Score: Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A)
Binary Subgroup Analysis
mITT Population

Month 9

Analysis Visit Statistics	Vutrisiran (HELIOS-A) (N=122)	Patisiran (HELIOS-A) (N=42)
No		
Patients included in analysis, N1	47	9
Improved, n(%)	2 (4.3)	0
No Change, n(%)	18 (38.3)	4 (44.4)
Worsened, n(%)	6 (12.8)	1 (11.1)
Missing, n(%)	21 (44.7)	4 (44.4)
Improved, (95% CI)	4.3 (0.0, 10.0)	0.0 (0.0, 0.0)
Percentage difference (Vutrisiran – Patisiran), (95% CI)	4.255 (-1.515, 10.026)	
Odds ratio (Vutrisiran/Patisiran), (95% CI) [1]	1.044 (0.046, 23.543)	
Relative risk (Vutrisiran/Patisiran), (95% CI) [1]	1.042 (0.054, 20.081)	
P-value [2]	0.9784	
p-value of Treatment*Previous Tetramer Stabilizer Use [3]	0.4243	

N1 = Patients with missing postbaseline values due to COVID-19 or after initiation of local standard treatment for hATTR amyloidosis were included in analysis.
[1] Based on unstratified analysis.
In estimation of the odds ratio and relative risk, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the percentage difference or p-value.
[2] p-value based on the Wald test testing whether the relative risk equals to 1.
[3] p-value from a logistic regression with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Table 9.2
Polyneuropathy Disability (PND) Score: Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A)
Binary Subgroup Analysis
mITT Population

Month 18

Analysis Visit Statistics	Vutrisiran (HELIOS-A) (N=122)	Patisiran (HELIOS-A) (N=42)
Previous Tetramer Stabilizer Use		
Yes		
Patients included in analysis, N1	75	33
Improved, n(%)	8 (10.7)	0
No Change, n(%)	52 (69.3)	26 (78.8)
Worsened, n(%)	11 (14.7)	5 (15.2)
Missing, n(%)	4 (5.3)	2 (6.1)
Improved, (95% CI)	10.7 (3.7, 17.7)	0.0 (0.0, 0.0)
Percentage difference (Vutrisiran – Patisiran), (95% CI)	10.667 (3.681, 17.653)	
Odds ratio (Vutrisiran/Patisiran), (95% CI) [1]	8.437 (0.473, 150.614)	
Relative risk (Vutrisiran/Patisiran), (95% CI) [1]	7.605 (0.452, 128.021)	
P-value [2]	0.1590	

N1 = Patients with missing postbaseline values due to COVID-19 or after initiation of local standard treatment for hATTR amyloidosis were included in analysis.
[1] Based on unstratified analysis.
In estimation of the odds ratio and relative risk, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the percentage difference or p-value.
[2] p-value based on the Wald test testing whether the relative risk equals to 1.
[3] p-value from a logistic regression with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Table 9.2
Polyneuropathy Disability (PND) Score: Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A)
Binary Subgroup Analysis
mITT Population

Month 18

Analysis Visit Statistics	Vutrisiran (HELIOS-A) (N=122)	Patisiran (HELIOS-A) (N=42)
No		
Patients included in analysis, N1	47	9
Improved, n(%)	5 (10.6)	1 (11.1)
No Change, n(%)	30 (63.8)	4 (44.4)
Worsened, n(%)	9 (19.1)	2 (22.2)
Missing, n(%)	3 (6.4)	2 (22.2)
Improved, (95% CI)	10.6 (1.8, 19.5)	11.1 (0.0, 31.6)
Percentage difference (Vutrisiran – Patisiran), (95% CI)	-0.473 (-22.817, 21.871)	
Odds ratio (Vutrisiran/Patisiran), (95% CI) [1]	0.952 (0.098, 9.276)	
Relative risk (Vutrisiran/Patisiran), (95% CI) [1]	0.957 (0.126, 7.255)	
P-value [2]	0.9664	
p-value of Treatment*Previous Tetramer Stabilizer Use [3]	0.1792	

N1 = Patients with missing postbaseline values due to COVID-19 or after initiation of local standard treatment for hATTR amyloidosis were included in analysis.
[1] Based on unstratified analysis.
In estimation of the odds ratio and relative risk, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the percentage difference or p-value.
[2] p-value based on the Wald test testing whether the relative risk equals to 1.
[3] p-value from a logistic regression with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Table 9.2
Polyneuropathy Disability (PND) Score: Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A)
Binary Subgroup Analysis
mITT Population

Month 9

Analysis Visit Statistics	Vutrisiran (HELIOS-A) (N=122)	Patisiran (HELIOS-A) (N=42)
Genotype		
V30M		
Patients included in analysis, N1	54	20
Improved, n(%)	6 (11.1)	0
No Change, n(%)	34 (63.0)	17 (85.0)
Worsened, n(%)	6 (11.1)	2 (10.0)
Missing, n(%)	8 (14.8)	1 (5.0)
Improved, (95% CI)	11.1 (2.7, 19.5)	0.0 (0.0, 0.0)
Percentage difference (Vutrisiran – Patisiran), (95% CI)	11.111 (2.729, 19.493)	
Odds ratio (Vutrisiran/Patisiran), (95% CI) [1]	5.495 (0.296, 102.128)	
Relative risk (Vutrisiran/Patisiran), (95% CI) [1]	4.964 (0.292, 84.293)	
P-value [2]	0.2675	

N1 = Patients with missing postbaseline values due to COVID-19 or after initiation of local standard treatment for hATTR amyloidosis were included in analysis.
[1] Based on unstratified analysis.
In estimation of the odds ratio and relative risk, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the percentage difference or p-value.
[2] p-value based on the Wald test testing whether the relative risk equals to 1.
[3] p-value from a logistic regression with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Table 9.2
Polyneuropathy Disability (PND) Score: Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A)
Binary Subgroup Analysis
mITT Population

Month 9

Analysis Visit Statistics	Vutrisiran (HELIOS-A) (N=122)	Patisiran (HELIOS-A) (N=42)
non-V30M		
Patients included in analysis, N1	68	22
Improved, n(%)	2 (2.9)	0
No Change, n(%)	38 (55.9)	12 (54.5)
Worsened, n(%)	8 (11.8)	3 (13.6)
Missing, n(%)	20 (29.4)	7 (31.8)
Improved, (95% CI)	2.9 (0.0, 7.0)	0.0 (0.0, 0.0)
Percentage difference (Vutrisiran – Patisiran), (95% CI)	2.941 (-1.075, 6.957)	
Odds ratio (Vutrisiran/Patisiran), (95% CI) [1]	1.692 (0.078, 36.580)	
Relative risk (Vutrisiran/Patisiran), (95% CI) [1]	1.667 (0.083, 33.458)	
P-value [2]	0.7385	
p-value of Treatment*Genotype [3]	0.5941	

N1 = Patients with missing postbaseline values due to COVID-19 or after initiation of local standard treatment for hATTR amyloidosis were included in analysis.
[1] Based on unstratified analysis.
In estimation of the odds ratio and relative risk, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the percentage difference or p-value.
[2] p-value based on the Wald test testing whether the relative risk equals to 1.
[3] p-value from a logistic regression with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Table 9.2
Polyneuropathy Disability (PND) Score: Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A)
Binary Subgroup Analysis
mITT Population

Month 18

Analysis Visit Statistics	Vutrisiran (HELIOS-A) (N=122)	Patisiran (HELIOS-A) (N=42)
Genotype		
V30M		
Patients included in analysis, N1	54	20
Improved, n(%)	7 (13.0)	1 (5.0)
No Change, n(%)	37 (68.5)	15 (75.0)
Worsened, n(%)	8 (14.8)	4 (20.0)
Missing, n(%)	2 (3.7)	0
Improved, (95% CI)	13.0 (4.0, 21.9)	5.0 (0.0, 14.6)
Percentage difference (Vutrisiran – Patisiran), (95% CI)	7.963 (-5.133, 21.059)	
Odds ratio (Vutrisiran/Patisiran), (95% CI) [1]	2.830 (0.326, 24.586)	
Relative risk (Vutrisiran/Patisiran), (95% CI) [1]	2.593 (0.340, 19.770)	
P-value [2]	0.3580	

N1 = Patients with missing postbaseline values due to COVID-19 or after initiation of local standard treatment for hATTR amyloidosis were included in analysis.
[1] Based on unstratified analysis.
In estimation of the odds ratio and relative risk, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the percentage difference or p-value.
[2] p-value based on the Wald test testing whether the relative risk equals to 1.
[3] p-value from a logistic regression with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Table 9.2
Polyneuropathy Disability (PND) Score: Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A)
Binary Subgroup Analysis
mITT Population

Month 18

Analysis Visit Statistics	Vutrisiran (HELIOS-A) (N=122)	Patisiran (HELIOS-A) (N=42)
non-V30M		
Patients included in analysis, N1	68	22
Improved, n(%)	6 (8.8)	0
No Change, n(%)	45 (66.2)	15 (68.2)
Worsened, n(%)	12 (17.6)	3 (13.6)
Missing, n(%)	5 (7.4)	4 (18.2)
Improved, (95% CI)	8.8 (2.1, 15.6)	0.0 (0.0, 0.0)
Percentage difference (Vutrisiran – Patisiran), (95% CI)	8.824 (2.082, 15.565)	
Odds ratio (Vutrisiran/Patisiran), (95% CI) [1]	4.680 (0.253, 86.472)	
Relative risk (Vutrisiran/Patisiran), (95% CI) [1]	4.333 (0.254, 73.981)	
P-value [2]	0.3111	
p-value of Treatment*Genotype [3]	0.6460	

N1 = Patients with missing postbaseline values due to COVID-19 or after initiation of local standard treatment for hATTR amyloidosis were included in analysis.
[1] Based on unstratified analysis.
In estimation of the odds ratio and relative risk, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the percentage difference or p-value.
[2] p-value based on the Wald test testing whether the relative risk equals to 1.
[3] p-value from a logistic regression with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Table 9.2
Polyneuropathy Disability (PND) Score: Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A)
Binary Subgroup Analysis
mITT Population

Month 9

Analysis Visit Statistics	Vutrisiran (HELIOS-A) (N=122)	Patisiran (HELIOS-A) (N=42)
FAP Stage		
I		
Patients included in analysis, N1	84	31
Improved, n(%)	6 (7.1)	0
No Change, n(%)	50 (59.5)	22 (71.0)
Worsened, n(%)	8 (9.5)	4 (12.9)
Missing, n(%)	20 (23.8)	5 (16.1)
Improved, (95% CI)	7.1 (1.6, 12.7)	0.0 (0.0, 0.0)
Percentage difference (Vutrisiran – Patisiran), (95% CI)	7.143 (1.635, 12.650)	
Odds ratio (Vutrisiran/Patisiran), (95% CI) [1]	5.217 (0.285, 95.376)	
Relative risk (Vutrisiran/Patisiran), (95% CI) [1]	4.894 (0.284, 84.403)	
P-value [2]	0.2744	

N1 = Patients with missing postbaseline values due to COVID-19 or after initiation of local standard treatment for hATTR amyloidosis were included in analysis.
[1] Based on unstratified analysis.
In estimation of the odds ratio and relative risk, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the percentage difference or p-value.
[2] p-value based on the Wald test testing whether the relative risk equals to 1.
[3] p-value from a logistic regression with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Table 9.2
Polyneuropathy Disability (PND) Score: Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A)
Binary Subgroup Analysis
mITT Population

Month 9

Analysis Visit Statistics	Vutrisiran (HELIOS-A) (N=122)	Patisiran (HELIOS-A) (N=42)
II&III		
Patients included in analysis, N1	38	11
Improved, n(%)	2 (5.3)	0
No Change, n(%)	22 (57.9)	7 (63.6)
Worsened, n(%)	6 (15.8)	1 (9.1)
Missing, n(%)	8 (21.1)	3 (27.3)
Improved, (95% CI)	5.3 (0.0, 12.4)	0.0 (0.0, 0.0)
Percentage difference (Vutrisiran- Patisiran), (95% CI)	5.263 (-1.837, 12.363)	
Odds ratio (Vutrisiran/Patisiran), (95% CI) [1]	1.575 (0.070, 35.245)	
Relative risk (Vutrisiran/Patisiran), (95% CI) [1]	1.538 (0.079, 29.887)	
P-value [2]	0.7759	
p-value of Treatment*FAP Stage [3]	0.5916	

N1 = Patients with missing postbaseline values due to COVID-19 or after initiation of local standard treatment for hATTR amyloidosis were included in analysis.
[1] Based on unstratified analysis.
In estimation of the odds ratio and relative risk, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the percentage difference or p-value.
[2] p-value based on the Wald test testing whether the relative risk equals to 1.
[3] p-value from a logistic regression with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

Alnylam Pharmaceuticals Inc.
ALN-TTRSC02-002

Table 9.2
Polyneuropathy Disability (PND) Score: Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A)
Binary Subgroup Analysis
mITT Population

Month 18

Analysis Visit Statistics	Vutrisiran (HELIOS-A) (N=122)	Patisiran (HELIOS-A) (N=42)
FAP Stage		
I		
Patients included in analysis, N1	84	31
Improved, n(%)	10 (11.9)	1 (3.2)
No Change, n(%)	61 (72.6)	23 (74.2)
Worsened, n(%)	10 (11.9)	6 (19.4)
Missing, n(%)	3 (3.6)	1 (3.2)
Improved, (95% CI)	11.9 (5.0, 18.8)	3.2 (0.0, 9.4)
Percentage difference (Vutrisiran- Patisiran), (95% CI)	8.679 (-0.629, 17.987)	
Odds ratio (Vutrisiran/Patisiran), (95% CI) [1]	4.054 (0.497, 33.071)	
Relative risk (Vutrisiran/Patisiran), (95% CI) [1]	3.690 (0.493, 27.652)	
P-value [2]	0.2038	

N1 = Patients with missing postbaseline values due to COVID-19 or after initiation of local standard treatment for hATTR amyloidosis were included in analysis.
[1] Based on unstratified analysis.
In estimation of the odds ratio and relative risk, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the percentage difference or p-value.
[2] p-value based on the Wald test testing whether the relative risk equals to 1.
[3] p-value from a logistic regression with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

Alnylam Pharmaceuticals Inc.
ALN-TTRSC02-002

Table 9.2
Polyneuropathy Disability (PND) Score: Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A)
Binary Subgroup Analysis
mITT Population

Month 18

Analysis Visit Statistics	Vutrisiran (HELIOS-A) (N=122)	Patisiran (HELIOS-A) (N=42)
II&III		
Patients included in analysis, N1	38	11
Improved, n(%)	3 (7.9)	0
No Change, n(%)	21 (55.3)	7 (63.6)
Worsened, n(%)	10 (26.3)	1 (9.1)
Missing, n(%)	4 (10.5)	3 (27.3)
Improved, (95% CI)	7.9 (0.0, 16.5)	0.0 (0.0, 0.0)
Percentage difference (Vutrisiran – Patisiran), (95% CI)	7.895 (-0.679, 16.468)	
Odds ratio (Vutrisiran/Patisiran), (95% CI) [1]	2.268 (0.109, 47.258)	
Relative risk (Vutrisiran/Patisiran), (95% CI) [1]	2.154 (0.120, 38.820)	
P-value [2]	0.6030	
p-value of Treatment*FAP Stage [3]	0.8994	

N1 = Patients with missing postbaseline values due to COVID-19 or after initiation of local standard treatment for hATTR amyloidosis were included in analysis.
[1] Based on unstratified analysis.
In estimation of the odds ratio and relative risk, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the percentage difference or p-value.
[2] p-value based on the Wald test testing whether the relative risk equals to 1.
[3] p-value from a logistic regression with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

Alnylam Pharmaceuticals Inc.
ALN-TTRSC02-002

Table 9.2
Polyneuropathy Disability (PND) Score: Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A)
Binary Subgroup Analysis
mITT Population

Month 9

Analysis Visit Statistics	Vutrisiran (HELIOS-A) (N=122)	Patisiran (HELIOS-A) (N=42)
Cardiac Subpopulation		
Yes		
Patients included in analysis, N1	40	14
Improved, n(%)	0	0
No Change, n(%)	28 (70.0)	11 (78.6)
Worsened, n(%)	5 (12.5)	2 (14.3)
Missing, n(%)	7 (17.5)	1 (7.1)
Improved, (95% CI)	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)
Percentage difference (Vutrisiran – Patisiran), (95% CI)	- (-,-)	
Odds ratio (Vutrisiran/Patisiran), (95% CI) [1]	0.358 (0.007, 18.886)	
Relative risk (Vutrisiran/Patisiran), (95% CI) [1]	0.366 (0.008, 17.629)	
P-value [2]	0.6110	

N1 = Patients with missing postbaseline values due to COVID-19 or after initiation of local standard treatment for hATTR amyloidosis were included in analysis.
[1] Based on unstratified analysis.
In estimation of the odds ratio and relative risk, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the percentage difference or p-value.
[2] p-value based on the Wald test testing whether the relative risk equals to 1.
[3] p-value from a logistic regression with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

Alnylam Pharmaceuticals Inc.
ALN-TTRSC02-002

Table 9.2
Polyneuropathy Disability (PND) Score: Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A)
Binary Subgroup Analysis
mITT Population

Month 9

Analysis Visit Statistics	Vutrisiran (HELIOS-A) (N=122)	Patisiran (HELIOS-A) (N=42)
No		
Patients included in analysis, N1	82	28
Improved, n(%)	8 (9.8)	0
No Change, n(%)	44 (53.7)	18 (64.3)
Worsened, n(%)	9 (11.0)	3 (10.7)
Missing, n(%)	21 (25.6)	7 (25.0)
Improved, (95% CI)	9.8 (3.3, 16.2)	0.0 (0.0, 0.0)
Percentage difference (Vutrisiran - Patisiran), (95% CI)	9.756 (3.334, 16.178)	
Odds ratio (Vutrisiran/Patisiran), (95% CI) [1]	6.503 (0.363, 116.393)	
Relative risk (Vutrisiran/Patisiran), (95% CI) [1]	5.940 (0.354, 99.716)	
P-value [2]	0.2157	
p-value of Treatment*Cardiac Subpopulation [3]	0.2566	

N1 = Patients with missing postbaseline values due to COVID-19 or after initiation of local standard treatment for hATTR amyloidosis were included in analysis.
[1] Based on unstratified analysis.
In estimation of the odds ratio and relative risk, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the percentage difference or p-value.
[2] p-value based on the Wald test testing whether the relative risk equals to 1.
[3] p-value from a logistic regression with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

Alnylam Pharmaceuticals Inc.
ALN-TTRSC02-002

Table 9.2
Polyneuropathy Disability (PND) Score: Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A)
Binary Subgroup Analysis
mITT Population

Month 18

Analysis Visit Statistics	Vutrisiran (HELIOS-A) (N=122)	Patisiran (HELIOS-A) (N=42)
Cardiac Subpopulation		
Yes		
Patients included in analysis, N1	40	14
Improved, n(%)	5 (12.5)	0
No Change, n(%)	25 (62.5)	13 (92.9)
Worsened, n(%)	7 (17.5)	0
Missing, n(%)	3 (7.5)	1 (7.1)
Improved, (95% CI)	12.5 (2.3, 22.7)	0.0 (0.0, 0.0)
Percentage difference (Vutrisiran – Patisiran), (95% CI)	12.500 (2.251, 22.749)	
Odds ratio (Vutrisiran/Patisiran), (95% CI) [1]	4.493 (0.233, 86.601)	
Relative risk (Vutrisiran/Patisiran), (95% CI) [1]	4.024 (0.237, 68.469)	
P-value [2]	0.3356	

N1 = Patients with missing postbaseline values due to COVID-19 or after initiation of local standard treatment for hATTR amyloidosis were included in analysis.
[1] Based on unstratified analysis.
In estimation of the odds ratio and relative risk, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the percentage difference or p-value.
[2] p-value based on the Wald test testing whether the relative risk equals to 1.
[3] p-value from a logistic regression with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Alnylam Pharmaceuticals Inc.
ALN-TTRSC02-002

Table 9.2
Polyneuropathy Disability (PND) Score: Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A)
Binary Subgroup Analysis
mITT Population

Month 18

Analysis Visit Statistics	Vutrisiran (HELIOS-A) (N=122)	Patisiran (HELIOS-A) (N=42)
No		
Patients included in analysis, N1	82	28
Improved, n(%)	8 (9.8)	1 (3.6)
No Change, n(%)	57 (69.5)	17 (60.7)
Worsened, n(%)	13 (15.9)	7 (25.0)
Missing, n(%)	4 (4.9)	3 (10.7)
Improved, (95% CI)	9.8 (3.3, 16.2)	3.6 (0.0, 10.4)
Percentage difference (Vutrisiran – Patisiran), (95% CI)	6.185 (-3.222, 15.592)	
Odds ratio (Vutrisiran/Patisiran), (95% CI) [1]	2.919 (0.349, 24.441)	
Relative risk (Vutrisiran/Patisiran), (95% CI) [1]	2.732 (0.357, 20.885)	
P-value [2]	0.3329	
p-value of Treatment*Cardiac Subpopulation [3]	0.6736	

N1 = Patients with missing postbaseline values due to COVID-19 or after initiation of local standard treatment for hATTR amyloidosis were included in analysis.
[1] Based on unstratified analysis.
In estimation of the odds ratio and relative risk, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the percentage difference or p-value.
[2] p-value based on the Wald test testing whether the relative risk equals to 1.
[3] p-value from a logistic regression with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

Alnylam Pharmaceuticals Inc.
ALN-TTRSC02-002

Table 9.2
Polyneuropathy Disability (PND) Score: Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A)
Binary Subgroup Analysis
mITT Population

Month 9

Analysis Visit Statistics	Vutrisiran (HELIOS-A) (N=122)	Patisiran (HELIOS-A) (N=42)
Weight (kg)		
<65 kg		
Patients included in analysis, N1	46	15
Improved, n(%)	3 (6.5)	0
No Change, n(%)	29 (63.0)	12 (80.0)
Worsened, n(%)	7 (15.2)	2 (13.3)
Missing, n(%)	7 (15.2)	1 (6.7)
Improved, (95% CI)	6.5 (0.0, 13.7)	0.0 (0.0, 0.0)
Percentage difference (Vutrisiran – Patisiran), (95% CI)	6.522 (-0.613, 13.657)	
Odds ratio (Vutrisiran/Patisiran), (95% CI) [1]	2.494 (0.122, 51.079)	
Relative risk (Vutrisiran/Patisiran), (95% CI) [1]	2.383 (0.130, 43.673)	
P-value [2]	0.5584	

N1 = Patients with missing postbaseline values due to COVID-19 or after initiation of local standard treatment for hATTR amyloidosis were included in analysis.
[1] Based on unstratified analysis.
In estimation of the odds ratio and relative risk, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the percentage difference or p-value.
[2] p-value based on the Wald test testing whether the relative risk equals to 1.
[3] p-value from a logistic regression with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

Alnylam Pharmaceuticals Inc.
ALN-TTRSC02-002

Table 9.2
Polyneuropathy Disability (PND) Score: Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A)
Binary Subgroup Analysis
mITT Population

Month 9

Analysis Visit Statistics	Vutrisiran (HELIOS-A) (N=122)	Patisiran (HELIOS-A) (N=42)
≥65 kg		
Patients included in analysis, N1	76	27
Improved, n(%)	5 (6.6)	0
No Change, n(%)	43 (56.6)	17 (63.0)
Worsened, n(%)	7 (9.2)	3 (11.1)
Missing, n(%)	21 (27.6)	7 (25.9)
Improved, (95% CI)	6.6 (1.0, 12.2)	0.0 (0.0, 0.0)
Percentage difference (Vutrisiran – Patisiran), (95% CI)	6.579 (1.005, 12.153)	
Odds ratio (Vutrisiran/Patisiran), (95% CI) [1]	4.231 (0.226, 79.096)	
Relative risk (Vutrisiran/Patisiran), (95% CI) [1]	4.000 (0.228, 70.026)	
P-value [2]	0.3425	
p-value of Treatment*Weight (kg) [3]	0.8100	

N1 = Patients with missing postbaseline values due to COVID-19 or after initiation of local standard treatment for hATTR amyloidosis were included in analysis.
[1] Based on unstratified analysis.
In estimation of the odds ratio and relative risk, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the percentage difference or p-value.
[2] p-value based on the Wald test testing whether the relative risk equals to 1.
[3] p-value from a logistic regression with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

Alnylam Pharmaceuticals Inc.
ALN-TTRSC02-002

Table 9.2
Polyneuropathy Disability (PND) Score: Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A)
Binary Subgroup Analysis
mITT Population

Month 18

Analysis Visit Statistics	Vutrisiran (HELIOS-A) (N=122)	Patisiran (HELIOS-A) (N=42)
Weight (kg)		
<65 kg		
Patients included in analysis, N1	46	15
Improved, n(%)	7 (15.2)	1 (6.7)
No Change, n(%)	27 (58.7)	11 (73.3)
Worsened, n(%)	8 (17.4)	3 (20.0)
Missing, n(%)	4 (8.7)	0
Improved, (95% CI)	15.2 (4.8, 25.6)	6.7 (0.0, 19.3)
Percentage difference (Vutrisiran – Patisiran), (95% CI)	8.551 (-7.792, 24.894)	
Odds ratio (Vutrisiran/Patisiran), (95% CI) [1]	2.513 (0.283, 22.284)	
Relative risk (Vutrisiran/Patisiran), (95% CI) [1]	2.283 (0.305, 17.080)	
P-value [2]	0.4216	

N1 = Patients with missing postbaseline values due to COVID-19 or after initiation of local standard treatment for hATTR amyloidosis were included in analysis.
[1] Based on unstratified analysis.
In estimation of the odds ratio and relative risk, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the percentage difference or p-value.
[2] p-value based on the Wald test testing whether the relative risk equals to 1.
[3] p-value from a logistic regression with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

Alnylam Pharmaceuticals Inc.
ALN-TTRSC02-002

Table 9.2
Polyneuropathy Disability (PND) Score: Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A)
Binary Subgroup Analysis
mITT Population

Month 18

Analysis Visit Statistics	Vutrisiran (HELIOS-A) (N=122)	Patisiran (HELIOS-A) (N=42)
≥65 kg		
Patients included in analysis, N1	76	27
Improved, n(%)	6 (7.9)	0
No Change, n(%)	55 (72.4)	19 (70.4)
Worsened, n(%)	12 (15.8)	4 (14.8)
Missing, n(%)	3 (3.9)	4 (14.8)
Improved, (95% CI)	7.9 (1.8, 14.0)	0.0 (0.0, 0.0)
Percentage difference (Vutrisiran – Patisiran), (95% CI)	7.895 (1.832, 13.957)	
Odds ratio (Vutrisiran/Patisiran), (95% CI) [1]	5.071 (0.276, 93.086)	
Relative risk (Vutrisiran/Patisiran), (95% CI) [1]	4.727 (0.275, 81.214)	
P-value [2]	0.2843	
p-value of Treatment*Weight (kg) [3]	0.5716	

N1 = Patients with missing postbaseline values due to COVID-19 or after initiation of local standard treatment for hATTR amyloidosis were included in analysis.
[1] Based on unstratified analysis.
In estimation of the odds ratio and relative risk, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the percentage difference or p-value.
[2] p-value based on the Wald test testing whether the relative risk equals to 1.
[3] p-value from a logistic regression with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

Subgruppenanalysen zum Endpunkt „Veränderung der kardialen Symptomatik gemessen anhand der Serumkonzentrationen des NT-proBNP, Troponin T und Troponin I“

NT-proBNP

Alnylam Pharmaceuticals Inc.
ALN-TTRSC02-002

Table 12.2
Cardiac Biomarkers - NT-proBNP (ng/L): Change from Baseline to Month 18, MMRM Model
Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A) Subgroup Analysis
mITT Population

Subgroup Visit	Adjusted Geometric Fold Change (95% CI) Vutrisiran (HELIOS-A) (N=122)	 Patisiran (HELIOS-A) (N=42)	Adjusted Geometric Fold Change Ratio (Vutrisiran/Patisiran) (95% CI), p-value	Standardized Effect Size (95% CI)
Age (years)				
<65	76	31		
Week 12	0.99 (0.87, 1.13)	0.88 (0.72, 1.09)	1.13 (0.88, 1.44), 0.3338	0.18 (-0.25, 0.61)
Week 24	0.95 (0.83, 1.08)	0.93 (0.75, 1.14)	1.02 (0.80, 1.30), 0.8698	0.03 (-0.39, 0.46)
Month 9	1.00 (0.88, 1.13)	1.12 (0.91, 1.37)	0.89 (0.70, 1.13), 0.3518	-0.20 (-0.63, 0.23)
Week 48	0.94 (0.81, 1.09)	1.00 (0.79, 1.27)	0.94 (0.71, 1.24), 0.6508	-0.09 (-0.52, 0.34)
Week 60	0.94 (0.82, 1.08)	1.00 (0.79, 1.25)	0.94 (0.72, 1.23), 0.6529	-0.09 (-0.53, 0.35)
Week 72	0.94 (0.81, 1.08)	0.98 (0.78, 1.23)	0.96 (0.73, 1.25), 0.7396	-0.07 (-0.50, 0.36)
Month 18	0.94 (0.81, 1.10)	1.03 (0.80, 1.31)	0.92 (0.69, 1.23), 0.5603	-0.11 (-0.54, 0.31)
≥65	44	10		
Week 12	1.02 (0.87, 1.20)	0.88 (0.63, 1.24)	1.16 (0.80, 1.67), 0.4333	0.32 (-0.39, 1.03)
Week 24	0.97 (0.83, 1.15)	0.93 (0.66, 1.30)	1.05 (0.73, 1.51), 0.8013	0.10 (-0.61, 0.80)
Month 9	1.02 (0.87, 1.20)	1.12 (0.80, 1.56)	0.92 (0.64, 1.32), 0.6390	-0.14 (-0.85, 0.57)
Week 48	0.97 (0.81, 1.16)	1.01 (0.71, 1.43)	0.96 (0.65, 1.42), 0.8504	-0.05 (-0.73, 0.63)
Week 60	0.96 (0.81, 1.14)	1.00 (0.71, 1.41)	0.97 (0.66, 1.41), 0.8604	-0.05 (-0.76, 0.65)
Week 72	0.96 (0.81, 1.14)	0.98 (0.69, 1.39)	0.98 (0.67, 1.44), 0.9241	-0.03 (-0.74, 0.68)
Month 18	0.97 (0.81, 1.16)	1.03 (0.72, 1.47)	0.94 (0.63, 1.40), 0.7707	-0.08 (-0.79, 0.63)
p-value of Treatment*Age	0.8965			

LS estimates and p-value derived from mixed-effects model for repeated measures (MMRM), controlling for categorical factors (treatment, visit), the subgroup variable, continuous covariate (baseline value), and interaction (treatment by visit, treatment by subgroup).
Standardized effect size (d) = LS mean difference/estimated pooled standard deviation with the small sample bias correction.

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

Alnylam Pharmaceuticals Inc.
ALN-TTRSC02-002

Table 12.2
Cardiac Biomarkers - NT-proBNP (ng/L): Change from Baseline to Month 18, MMRM Model
Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A) Subgroup Analysis
mITT Population

Subgroup Visit	Adjusted Geometric Fold Change (95% CI) Vutrisiran (HELIOS-A) (N=122)	 Patisiran (HELIOS-A) (N=42)	Adjusted Geometric Fold Change Ratio (Vutrisiran/Patisiran) (95% CI), p-value	Standardized Effect Size (95% CI)
Sex				
Male	77	26		
Week 12	1.01 (0.89, 1.15)	0.90 (0.72, 1.12)	1.12 (0.87, 1.45), 0.3640	0.20 (-0.25, 0.66)
Week 24	0.96 (0.84, 1.09)	0.94 (0.75, 1.18)	1.02 (0.79, 1.32), 0.8864	0.04 (-0.41, 0.49)
Month 9	1.01 (0.89, 1.15)	1.13 (0.91, 1.41)	0.89 (0.69, 1.15), 0.3667	-0.20 (-0.66, 0.26)
Week 48	0.95 (0.83, 1.10)	1.02 (0.79, 1.31)	0.94 (0.70, 1.25), 0.6526	-0.09 (-0.54, 0.36)
Week 60	0.95 (0.83, 1.09)	1.01 (0.80, 1.29)	0.94 (0.71, 1.24), 0.6552	-0.09 (-0.56, 0.38)
Week 72	0.95 (0.83, 1.09)	1.00 (0.78, 1.27)	0.95 (0.72, 1.26), 0.7384	-0.08 (-0.54, 0.39)
Month 18	0.96 (0.82, 1.11)	1.04 (0.80, 1.35)	0.92 (0.68, 1.23), 0.5645	-0.13 (-0.59, 0.34)
Female	43	15		
Week 12	1.00 (0.85, 1.17)	0.86 (0.65, 1.13)	1.16 (0.84, 1.60), 0.3536	0.24 (-0.36, 0.83)
Week 24	0.95 (0.81, 1.12)	0.90 (0.68, 1.19)	1.05 (0.76, 1.45), 0.7517	0.07 (-0.55, 0.68)
Month 9	1.00 (0.85, 1.17)	1.09 (0.83, 1.43)	0.92 (0.67, 1.26), 0.6075	-0.14 (-0.74, 0.46)
Week 48	0.95 (0.79, 1.13)	0.98 (0.73, 1.32)	0.97 (0.68, 1.37), 0.8511	-0.05 (-0.65, 0.55)
Week 60	0.94 (0.80, 1.11)	0.97 (0.73, 1.30)	0.97 (0.69, 1.36), 0.8626	-0.05 (-0.66, 0.57)
Week 72	0.94 (0.79, 1.12)	0.95 (0.71, 1.28)	0.99 (0.70, 1.38), 0.9341	-0.02 (-0.61, 0.58)
Month 18	0.95 (0.79, 1.13)	1.00 (0.74, 1.36)	0.95 (0.66, 1.35), 0.7630	-0.07 (-0.65, 0.52)
p-value of Treatment*Sex	0.8601			

LS estimates and p-value derived from mixed-effects model for repeated measures (MMRM), controlling for categorical factors (treatment, visit), the subgroup variable, continuous covariate (baseline value), and interaction (treatment by visit, treatment by subgroup).
Standardized effect size (d) = LS mean difference/estimated pooled standard deviation with the small sample bias correction.

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Table 12.2
Cardiac Biomarkers - NT-proBNP (ng/L): Change from Baseline to Month 18, MMRM Model
Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A) Subgroup Analysis
mITT Population

Subgroup Visit	Adjusted Geometric Fold Change (95% CI) Vutrisiran (HELIOS-A) (N=122)	 Patisiran (HELIOS-A) (N=42)	Adjusted Geometric Fold Change Ratio (Vutrisiran/Patisiran) (95% CI), p-value	Standardized Effect Size (95% CI)
Race				
White	84	28		
Week 12	1.01 (0.90, 1.15)	0.83 (0.67, 1.03)	1.22 (0.95, 1.57), 0.1111	0.32 (-0.12, 0.77)
Week 24	0.96 (0.85, 1.09)	0.87 (0.70, 1.08)	1.11 (0.86, 1.42), 0.4276	0.16 (-0.27, 0.59)
Month 9	1.01 (0.90, 1.15)	1.05 (0.85, 1.29)	0.97 (0.76, 1.23), 0.7780	-0.07 (-0.50, 0.37)
Week 48	0.96 (0.83, 1.10)	0.94 (0.74, 1.20)	1.02 (0.77, 1.35), 0.9107	0.02 (-0.40, 0.45)
Week 60	0.95 (0.84, 1.09)	0.94 (0.74, 1.18)	1.02 (0.78, 1.33), 0.8869	0.03 (-0.42, 0.48)
Week 72	0.95 (0.83, 1.09)	0.92 (0.73, 1.16)	1.04 (0.79, 1.36), 0.7998	0.05 (-0.39, 0.49)
Month 18	0.96 (0.83, 1.11)	0.96 (0.75, 1.24)	0.99 (0.74, 1.33), 0.9718	-0.01 (-0.44, 0.43)
All Other Races	36	13		
Week 12	0.99 (0.83, 1.17)	1.01 (0.75, 1.35)	0.98 (0.70, 1.37), 0.8924	-0.04 (-0.67, 0.58)
Week 24	0.94 (0.79, 1.12)	1.06 (0.79, 1.43)	0.88 (0.63, 1.25), 0.4760	-0.21 (-0.88, 0.46)
Month 9	0.99 (0.83, 1.17)	1.28 (0.95, 1.72)	0.77 (0.55, 1.08), 0.1345	-0.37 (-1.05, 0.30)
Week 48	0.93 (0.77, 1.13)	1.15 (0.84, 1.58)	0.81 (0.56, 1.17), 0.2633	-0.28 (-0.95, 0.38)
Week 60	0.93 (0.77, 1.11)	1.14 (0.84, 1.55)	0.81 (0.57, 1.17), 0.2595	-0.30 (-0.97, 0.37)
Week 72	0.93 (0.77, 1.11)	1.12 (0.82, 1.53)	0.83 (0.58, 1.18), 0.2980	-0.31 (-0.97, 0.36)
Month 18	0.93 (0.77, 1.13)	1.18 (0.85, 1.62)	0.79 (0.55, 1.16), 0.2279	-0.31 (-0.98, 0.36)
p-value of Treatment*Race	0.2492			

LS estimates and p-value derived from mixed-effects model for repeated measures (MMRM), controlling for categorical factors (treatment, visit), the subgroup variable, continuous covariate (baseline value), and interaction (treatment by visit, treatment by subgroup).
Standardized effect size (d) = LS mean difference/estimated pooled standard deviation with the small sample bias correction.

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Table 12.2
Cardiac Biomarkers - NT-proBNP (ng/L): Change from Baseline to Month 18, MMRM Model
Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A) Subgroup Analysis
mITT Population

Subgroup Visit	Adjusted Geometric Fold Change (95% CI) Vutrisiran (HELIOS-A) (N=122)	 Patisiran (HELIOS-A) (N=42)	Adjusted Geometric Fold Change Ratio (Vutrisiran/Patisiran) (95% CI), p-value	Standardized Effect Size (95% CI)
Region				
North America	27	8		
Week 12	0.81 (0.67, 0.99)	0.81 (0.56, 1.15)	1.01 (0.67, 1.52), 0.9708	0.01 (-0.76, 0.78)
Week 24	0.77 (0.63, 0.94)	0.85 (0.59, 1.21)	0.91 (0.60, 1.38), 0.6609	-0.14 (-0.91, 0.64)
Month 9	0.81 (0.67, 0.99)	1.02 (0.71, 1.45)	0.80 (0.53, 1.20), 0.2774	-0.45 (-1.28, 0.39)
Week 48	0.77 (0.62, 0.95)	0.92 (0.63, 1.33)	0.84 (0.55, 1.29), 0.4211	-0.25 (-1.02, 0.53)
Week 60	0.77 (0.62, 0.94)	0.91 (0.63, 1.32)	0.84 (0.55, 1.29), 0.4237	-0.21 (-1.03, 0.60)
Week 72	0.76 (0.62, 0.94)	0.89 (0.62, 1.30)	0.86 (0.56, 1.31), 0.4703	-0.20 (-1.07, 0.67)
Month 18	0.77 (0.62, 0.95)	0.94 (0.64, 1.37)	0.82 (0.53, 1.27), 0.3758	-0.29 (-1.11, 0.53)
Western Europe	40	19		
Week 12	0.99 (0.84, 1.16)	0.87 (0.68, 1.12)	1.13 (0.84, 1.52), 0.4108	0.21 (-0.36, 0.77)
Week 24	0.94 (0.79, 1.11)	0.91 (0.71, 1.17)	1.03 (0.76, 1.38), 0.8702	0.04 (-0.54, 0.61)
Month 9	0.99 (0.84, 1.16)	1.10 (0.86, 1.40)	0.90 (0.67, 1.20), 0.4615	-0.19 (-0.75, 0.36)
Week 48	0.93 (0.78, 1.12)	0.99 (0.76, 1.30)	0.94 (0.68, 1.30), 0.7188	-0.08 (-0.65, 0.48)
Week 60	0.93 (0.78, 1.11)	0.98 (0.75, 1.28)	0.95 (0.69, 1.30), 0.7265	-0.10 (-0.67, 0.48)
Week 72	0.93 (0.78, 1.10)	0.97 (0.74, 1.26)	0.96 (0.70, 1.32), 0.8049	-0.07 (-0.61, 0.48)
Month 18	0.93 (0.78, 1.12)	1.01 (0.76, 1.34)	0.92 (0.66, 1.29), 0.6347	-0.11 (-0.66, 0.45)

LS estimates and p-value derived from mixed-effects model for repeated measures (MMRM), controlling for categorical factors (treatment, visit), the subgroup variable, continuous covariate (baseline value), and interaction (treatment by visit, treatment by subgroup).
Standardized effect size (d) = LS mean difference/estimated pooled standard deviation with the small sample bias correction.

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Table 12.2
Cardiac Biomarkers - NT-proBNP (ng/L): Change from Baseline to Month 18, MMRM Model
Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A) Subgroup Analysis
mITT Population

Subgroup Visit	Adjusted Geometric Fold Change (95% CI) Vutrisiran (HELIOS-A) (N=122)	 Patisiran (HELIOS-A) (N=42)	Adjusted Geometric Fold Change Ratio (Vutrisiran/Patisiran) (95% CI), p-value	Standardized Effect Size (95% CI)
Rest of World	53	14		
Week 12	1.13 (0.98, 1.31)	0.95 (0.72, 1.25)	1.20 (0.87, 1.64), 0.2650	0.34 (-0.26, 0.94)
Week 24	1.08 (0.93, 1.25)	1.00 (0.75, 1.32)	1.08 (0.79, 1.49), 0.6201	0.15 (-0.43, 0.74)
Month 9	1.13 (0.98, 1.31)	1.20 (0.91, 1.58)	0.95 (0.69, 1.29), 0.7286	-0.09 (-0.69, 0.51)
Week 48	1.07 (0.91, 1.26)	1.08 (0.80, 1.46)	1.00 (0.71, 1.40), 0.9795	-0.01 (-0.59, 0.58)
Week 60	1.07 (0.91, 1.25)	1.07 (0.80, 1.44)	1.00 (0.71, 1.40), 0.9921	-0.00 (-0.62, 0.62)
Week 72	1.07 (0.91, 1.25)	1.05 (0.78, 1.41)	1.02 (0.73, 1.42), 0.9275	0.02 (-0.58, 0.62)
Month 18	1.07 (0.91, 1.27)	1.10 (0.81, 1.50)	0.97 (0.68, 1.38), 0.8822	-0.03 (-0.64, 0.57)
p-value of Treatment*Region	0.7872			

LS estimates and p-value derived from mixed-effects model for repeated measures (MMRM), controlling for categorical factors (treatment, visit), the subgroup variable, continuous covariate (baseline value), and interaction (treatment by visit, treatment by subgroup).
Standardized effect size (d) = LS mean difference/estimated pooled standard deviation with the small sample bias correction.

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Table 12.2
Cardiac Biomarkers - NT-proBNP (ng/L): Change from Baseline to Month 18, MMRM Model
Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A) Subgroup Analysis
mITT Population

Subgroup Visit	Adjusted Geometric Fold Change (95% CI) Vutrisiran (HELIOS-A) (N=122)	 Patisiran (HELIOS-A) (N=42)	Adjusted Geometric Fold Change Ratio (Vutrisiran/Patisiran) (95% CI), p-value	Standardized Effect Size (95% CI)
Baseline NIS				
<50	78	27		
Week 12	0.96 (0.84, 1.09)	0.88 (0.71, 1.09)	1.09 (0.85, 1.40), 0.4974	0.13 (-0.32, 0.57)
Week 24	0.91 (0.80, 1.04)	0.92 (0.74, 1.15)	0.99 (0.77, 1.27), 0.9197	-0.02 (-0.45, 0.42)
Month 9	0.96 (0.84, 1.09)	1.11 (0.90, 1.37)	0.86 (0.68, 1.11), 0.2423	-0.25 (-0.70, 0.20)
Week 48	0.91 (0.78, 1.05)	1.00 (0.78, 1.28)	0.91 (0.68, 1.21), 0.5004	-0.13 (-0.57, 0.31)
Week 60	0.90 (0.79, 1.03)	0.99 (0.78, 1.25)	0.91 (0.69, 1.19), 0.4951	-0.14 (-0.60, 0.32)
Week 72	0.90 (0.78, 1.03)	0.97 (0.77, 1.24)	0.92 (0.70, 1.22), 0.5729	-0.11 (-0.56, 0.34)
Month 18	0.91 (0.78, 1.05)	1.02 (0.79, 1.31)	0.89 (0.66, 1.19), 0.4261	-0.16 (-0.61, 0.28)
≥50	42	14		
Week 12	1.10 (0.93, 1.30)	0.89 (0.67, 1.19)	1.23 (0.89, 1.70), 0.2133	0.54 (-0.09, 1.16)
Week 24	1.04 (0.89, 1.23)	0.94 (0.70, 1.25)	1.11 (0.80, 1.55), 0.5223	0.25 (-0.40, 0.91)
Month 9	1.10 (0.93, 1.29)	1.13 (0.85, 1.50)	0.97 (0.70, 1.35), 0.8720	-0.05 (-0.67, 0.57)
Week 48	1.04 (0.87, 1.24)	1.02 (0.75, 1.38)	1.02 (0.72, 1.46), 0.8994	0.04 (-0.60, 0.67)
Week 60	1.03 (0.87, 1.23)	1.01 (0.75, 1.36)	1.03 (0.73, 1.45), 0.8810	0.04 (-0.59, 0.68)
Week 72	1.03 (0.87, 1.23)	0.99 (0.73, 1.34)	1.04 (0.74, 1.47), 0.8129	0.07 (-0.57, 0.70)
Month 18	1.04 (0.87, 1.25)	1.04 (0.76, 1.42)	1.00 (0.70, 1.44), 0.9933	0.00 (-0.63, 0.64)
p-value of Treatment*Baseline NIS	0.5260			

LS estimates and p-value derived from mixed-effects model for repeated measures (MMRM), controlling for categorical factors (treatment, visit), the subgroup variable, continuous covariate (baseline value), and interaction (treatment by visit, treatment by subgroup).
Standardized effect size (d) = LS mean difference/estimated pooled standard deviation with the small sample bias correction.

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Table 12.2
Cardiac Biomarkers - NT-proBNP (ng/L): Change from Baseline to Month 18, MMRM Model
Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A) Subgroup Analysis
mITT Population

Subgroup Visit	Adjusted Geometric Fold Change (95% CI) Vutrisiran (HELIOS-A) (N=122)	 Patisiran (HELIOS-A) (N=42)	Adjusted Geometric Fold Change Ratio (Vutrisiran/Patisiran) (95% CI), p-value	Standardized Effect Size (95% CI)
Previous Tetramer Stabilizer Use				
Yes	74	33		
Week 12	0.99 (0.87, 1.12)	0.89 (0.72, 1.08)	1.12 (0.88, 1.42), 0.3675	0.19 (-0.24, 0.61)
Week 24	0.94 (0.83, 1.07)	0.93 (0.76, 1.14)	1.01 (0.79, 1.29), 0.9283	0.02 (-0.40, 0.44)
Month 9	0.99 (0.87, 1.12)	1.12 (0.92, 1.36)	0.88 (0.70, 1.12), 0.3064	-0.22 (-0.63, 0.20)
Week 48	0.94 (0.81, 1.08)	1.01 (0.80, 1.27)	0.93 (0.71, 1.22), 0.6003	-0.12 (-0.54, 0.30)
Week 60	0.93 (0.81, 1.07)	1.00 (0.80, 1.25)	0.93 (0.72, 1.21), 0.6004	-0.11 (-0.53, 0.32)
Week 72	0.93 (0.81, 1.07)	0.98 (0.78, 1.23)	0.95 (0.73, 1.23), 0.6855	-0.08 (-0.50, 0.34)
Month 18	0.94 (0.80, 1.09)	1.03 (0.81, 1.31)	0.91 (0.68, 1.21), 0.5149	-0.13 (-0.55, 0.29)
No	46	8		
Week 12	1.03 (0.88, 1.21)	0.87 (0.61, 1.26)	1.18 (0.79, 1.76), 0.4070	0.26 (-0.48, 1.00)
Week 24	0.98 (0.84, 1.15)	0.92 (0.64, 1.32)	1.07 (0.72, 1.59), 0.7357	0.12 (-0.62, 0.86)
Month 9	1.03 (0.88, 1.21)	1.10 (0.77, 1.59)	0.94 (0.63, 1.40), 0.7483	-0.11 (-0.95, 0.74)
Week 48	0.98 (0.82, 1.16)	0.99 (0.68, 1.46)	0.98 (0.65, 1.50), 0.9401	-0.02 (-0.76, 0.72)
Week 60	0.97 (0.83, 1.15)	0.99 (0.68, 1.44)	0.99 (0.65, 1.49), 0.9518	-0.02 (-0.86, 0.82)
Week 72	0.97 (0.82, 1.15)	0.97 (0.66, 1.42)	1.00 (0.66, 1.52), 0.9893	0.00 (-0.78, 0.79)
Month 18	0.98 (0.82, 1.17)	1.02 (0.69, 1.50)	0.96 (0.63, 1.47), 0.8627	-0.05 (-0.84, 0.73)
p-value of Treatment*Previous Tetramer Stabilizer Use	0.7939			

LS estimates and p-value derived from mixed-effects model for repeated measures (MMRM), controlling for categorical factors (treatment, visit), the subgroup variable, continuous covariate (baseline value), and interaction (treatment by visit, treatment by subgroup).
Standardized effect size (d) = LS mean difference/estimated pooled standard deviation with the small sample bias correction.
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Cardiac Biomarkers - NT-proBNP (ng/L): Change from Baseline to Month 18, MMRM Model
Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A) Subgroup Analysis
mITT Population

Subgroup Visit	Adjusted Geometric Fold Change (95% CI) Vutrisiran (HELIOS-A) (N=122)	 Patisiran (HELIOS-A) (N=42)	Adjusted Geometric Fold Change Ratio (Vutrisiran/Patisiran) (95% CI), p-value	Standardized Effect Size (95% CI)
Genotype				
V30M	53	20		
Week 12	0.98 (0.84, 1.13)	0.73 (0.57, 0.93)	1.33 (1.00, 1.77), 0.0476	0.46 (-0.08, 0.99)
Week 24	0.93 (0.80, 1.08)	0.77 (0.60, 0.98)	1.21 (0.91, 1.60), 0.1904	0.30 (-0.23, 0.83)
Month 9	0.98 (0.84, 1.13)	0.93 (0.73, 1.17)	1.05 (0.80, 1.39), 0.7104	0.09 (-0.43, 0.61)
Week 48	0.92 (0.78, 1.09)	0.83 (0.64, 1.09)	1.11 (0.81, 1.51), 0.5172	0.13 (-0.39, 0.66)
Week 60	0.92 (0.79, 1.07)	0.83 (0.64, 1.07)	1.11 (0.82, 1.50), 0.4846	0.16 (-0.38, 0.70)
Week 72	0.92 (0.78, 1.08)	0.81 (0.63, 1.06)	1.13 (0.83, 1.52), 0.4362	0.17 (-0.34, 0.68)
Month 18	0.92 (0.78, 1.09)	0.85 (0.65, 1.12)	1.08 (0.79, 1.49), 0.6164	0.10 (-0.41, 0.62)
non-V30M	67	21		
Week 12	1.03 (0.90, 1.18)	1.06 (0.83, 1.34)	0.97 (0.74, 1.28), 0.8429	-0.05 (-0.54, 0.45)
Week 24	0.98 (0.86, 1.12)	1.11 (0.88, 1.41)	0.88 (0.67, 1.16), 0.3582	-0.22 (-0.72, 0.28)
Month 9	1.03 (0.90, 1.17)	1.34 (1.06, 1.69)	0.77 (0.59, 1.01), 0.0548	-0.46 (-0.98, 0.05)
Week 48	0.97 (0.84, 1.13)	1.20 (0.93, 1.57)	0.81 (0.60, 1.09), 0.1648	-0.33 (-0.83, 0.16)
Week 60	0.97 (0.84, 1.12)	1.19 (0.92, 1.54)	0.81 (0.61, 1.09), 0.1580	-0.33 (-0.85, 0.19)
Week 72	0.97 (0.84, 1.12)	1.18 (0.91, 1.52)	0.82 (0.61, 1.10), 0.1915	-0.31 (-0.84, 0.22)
Month 18	0.97 (0.83, 1.14)	1.23 (0.94, 1.61)	0.79 (0.58, 1.08), 0.1412	-0.34 (-0.86, 0.18)
p-value of Treatment*Genotype	0.0774			

LS estimates and p-value derived from mixed-effects model for repeated measures (MMRM), controlling for categorical factors (treatment, visit), the subgroup variable, continuous covariate (baseline value), and interaction (treatment by visit, treatment by subgroup).
Standardized effect size (d) = LS mean difference/estimated pooled standard deviation with the small sample bias correction.

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Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A) Subgroup Analysis
mITT Population

Subgroup Visit	Adjusted Geometric Fold Change (95% CI) Vutrisiran (HELIOS-A) (N=122)	 Patisiran (HELIOS-A) (N=42)	Adjusted Geometric Fold Change Ratio (Vutrisiran/Patisiran) (95% CI), p-value	Standardized Effect Size (95% CI)
FAP Stage				
I	84	30		
Week 12	0.95 (0.83, 1.07)	0.86 (0.70, 1.07)	1.09 (0.86, 1.40), 0.4651	0.13 (-0.30, 0.56)
Week 24	0.90 (0.79, 1.02)	0.91 (0.74, 1.12)	0.99 (0.78, 1.26), 0.9371	-0.01 (-0.43, 0.40)
Month 9	0.95 (0.84, 1.07)	1.09 (0.89, 1.34)	0.87 (0.69, 1.10), 0.2290	-0.23 (-0.66, 0.19)
Week 48	0.89 (0.78, 1.03)	0.98 (0.78, 1.24)	0.91 (0.69, 1.19), 0.4941	-0.13 (-0.54, 0.29)
Week 60	0.89 (0.78, 1.02)	0.98 (0.78, 1.22)	0.91 (0.70, 1.19), 0.4931	-0.13 (-0.56, 0.31)
Week 72	0.89 (0.78, 1.02)	0.96 (0.76, 1.21)	0.93 (0.71, 1.21), 0.5733	-0.11 (-0.53, 0.31)
Month 18	0.90 (0.77, 1.04)	1.00 (0.79, 1.28)	0.89 (0.67, 1.18), 0.4242	-0.15 (-0.57, 0.27)
II&III	36	11		
Week 12	1.15 (0.96, 1.38)	0.94 (0.68, 1.29)	1.23 (0.86, 1.76), 0.2613	0.57 (-0.11, 1.25)
Week 24	1.10 (0.91, 1.32)	0.99 (0.71, 1.36)	1.11 (0.77, 1.60), 0.5692	0.29 (-0.46, 1.05)
Month 9	1.15 (0.96, 1.38)	1.19 (0.86, 1.64)	0.97 (0.68, 1.39), 0.8742	-0.07 (-0.79, 0.66)
Week 48	1.09 (0.90, 1.32)	1.07 (0.76, 1.50)	1.02 (0.70, 1.50), 0.9181	0.04 (-0.68, 0.76)
Week 60	1.08 (0.90, 1.31)	1.06 (0.76, 1.48)	1.02 (0.70, 1.49), 0.9008	0.06 (-0.69, 0.81)
Week 72	1.08 (0.90, 1.31)	1.04 (0.74, 1.46)	1.04 (0.71, 1.52), 0.8378	0.07 (-0.68, 0.82)
Month 18	1.09 (0.90, 1.33)	1.09 (0.77, 1.54)	1.00 (0.68, 1.48), 0.9977	-0.00 (-0.76, 0.75)
p-value of Treatment*FAP Stage	0.5693			

LS estimates and p-value derived from mixed-effects model for repeated measures (MMRM), controlling for categorical factors (treatment, visit), the subgroup variable, continuous covariate (baseline value), and interaction (treatment by visit, treatment by subgroup).
Standardized effect size (d) = LS mean difference/estimated pooled standard deviation with the small sample bias correction.

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Table 12.2
Cardiac Biomarkers - NT-proBNP (ng/L): Change from Baseline to Month 18, MMRM Model
Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A) Subgroup Analysis
mITT Population

Subgroup Visit	Adjusted Geometric Fold Change (95% CI) Vutrisiran (HELIOS-A) (N=122)	 Patisiran (HELIOS-A) (N=42)	Adjusted Geometric Fold Change Ratio (Vutrisiran/Patisiran) (95% CI), p-value	Standardized Effect Size (95% CI)
Cardiac Subpopulation				
Yes	39	14		
Week 12	1.08 (0.91, 1.28)	0.93 (0.70, 1.24)	1.16 (0.83, 1.61), 0.3759	0.24 (-0.40, 0.88)
Week 24	1.03 (0.86, 1.22)	0.98 (0.73, 1.30)	1.05 (0.76, 1.46), 0.7671	0.09 (-0.53, 0.70)
Month 9	1.08 (0.91, 1.28)	1.18 (0.88, 1.56)	0.92 (0.66, 1.27), 0.6119	-0.14 (-0.76, 0.48)
Week 48	1.02 (0.85, 1.23)	1.06 (0.78, 1.44)	0.97 (0.68, 1.38), 0.8482	-0.05 (-0.65, 0.56)
Week 60	1.02 (0.85, 1.22)	1.05 (0.78, 1.42)	0.97 (0.69, 1.37), 0.8591	-0.05 (-0.67, 0.57)
Week 72	1.02 (0.85, 1.22)	1.03 (0.76, 1.40)	0.98 (0.70, 1.39), 0.9294	-0.02 (-0.64, 0.60)
Month 18	1.02 (0.85, 1.24)	1.08 (0.79, 1.48)	0.95 (0.66, 1.36), 0.7610	-0.07 (-0.70, 0.55)
No	81	27		
Week 12	0.97 (0.85, 1.10)	0.86 (0.69, 1.07)	1.13 (0.88, 1.45), 0.3443	0.20 (-0.24, 0.64)
Week 24	0.92 (0.81, 1.05)	0.90 (0.72, 1.13)	1.02 (0.79, 1.32), 0.8680	0.03 (-0.41, 0.48)
Month 9	0.97 (0.86, 1.10)	1.09 (0.88, 1.35)	0.89 (0.70, 1.14), 0.3707	-0.20 (-0.65, 0.25)
Week 48	0.92 (0.79, 1.06)	0.98 (0.76, 1.25)	0.94 (0.71, 1.25), 0.6630	-0.09 (-0.54, 0.36)
Week 60	0.91 (0.80, 1.05)	0.97 (0.76, 1.23)	0.94 (0.72, 1.24), 0.6677	-0.09 (-0.56, 0.38)
Week 72	0.91 (0.79, 1.05)	0.95 (0.75, 1.21)	0.96 (0.73, 1.26), 0.7527	-0.07 (-0.52, 0.38)
Month 18	0.92 (0.79, 1.07)	1.00 (0.77, 1.29)	0.92 (0.68, 1.23), 0.5730	-0.12 (-0.56, 0.33)
p-value of Treatment*Cardiac Subpopulation	0.8813			

LS estimates and p-value derived from mixed-effects model for repeated measures (MMRM), controlling for categorical factors (treatment, visit), the subgroup variable, continuous covariate (baseline value), and interaction (treatment by visit, treatment by subgroup).
Standardized effect size (d) = LS mean difference/estimated pooled standard deviation with the small sample bias correction.

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Table 12.2
Cardiac Biomarkers - NT-proBNP (ng/L): Change from Baseline to Month 18, MMRM Model
Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A) Subgroup Analysis
mITT Population

Subgroup Visit	Adjusted Geometric Fold Change (95% CI) Vutrisiran (HELIOS-A) (N=122)	 Patisiran (HELIOS-A) (N=42)	Adjusted Geometric Fold Change Ratio (Vutrisiran/Patisiran) (95% CI), p-value	Standardized Effect Size (95% CI)
Weight (kg)				
<65	45	15		
Week 12	0.97 (0.83, 1.14)	0.89 (0.67, 1.17)	1.10 (0.80, 1.51), 0.5764	0.19 (-0.40, 0.78)
Week 24	0.93 (0.79, 1.09)	0.93 (0.71, 1.23)	0.99 (0.72, 1.37), 0.9594	-0.01 (-0.62, 0.59)
Month 9	0.97 (0.83, 1.14)	1.12 (0.86, 1.48)	0.87 (0.63, 1.19), 0.3766	-0.21 (-0.81, 0.38)
Week 48	0.92 (0.77, 1.10)	1.01 (0.75, 1.36)	0.91 (0.65, 1.29), 0.5983	-0.14 (-0.73, 0.46)
Week 60	0.92 (0.78, 1.08)	1.00 (0.75, 1.34)	0.91 (0.65, 1.28), 0.6011	-0.13 (-0.74, 0.48)
Week 72	0.92 (0.77, 1.09)	0.99 (0.74, 1.32)	0.93 (0.66, 1.30), 0.6668	-0.11 (-0.70, 0.49)
Month 18	0.92 (0.77, 1.10)	1.03 (0.76, 1.40)	0.89 (0.63, 1.27), 0.5271	-0.14 (-0.72, 0.44)
≥65	75	26		
Week 12	1.03 (0.90, 1.17)	0.88 (0.70, 1.10)	1.17 (0.90, 1.51), 0.2412	0.23 (-0.23, 0.69)
Week 24	0.98 (0.86, 1.11)	0.92 (0.74, 1.15)	1.06 (0.82, 1.37), 0.6783	0.09 (-0.37, 0.54)
Month 9	1.03 (0.90, 1.17)	1.11 (0.89, 1.38)	0.92 (0.72, 1.19), 0.5394	-0.15 (-0.62, 0.31)
Week 48	0.97 (0.84, 1.12)	1.00 (0.78, 1.28)	0.97 (0.73, 1.30), 0.8404	-0.04 (-0.49, 0.41)
Week 60	0.97 (0.84, 1.11)	0.99 (0.78, 1.26)	0.97 (0.74, 1.29), 0.8514	-0.04 (-0.51, 0.43)
Week 72	0.97 (0.84, 1.11)	0.98 (0.77, 1.24)	0.99 (0.75, 1.31), 0.9378	-0.02 (-0.48, 0.45)
Month 18	0.97 (0.83, 1.13)	1.02 (0.79, 1.32)	0.95 (0.70, 1.28), 0.7375	-0.07 (-0.54, 0.39)
p-value of Treatment*Weight	0.7411			

LS estimates and p-value derived from mixed-effects model for repeated measures (MMRM), with change from baseline in log-transformed NT-proBNP as the outcome variable, controlling for categorical factors (treatment, visit), the subgroup variable, continuous covariate (log-transformed baseline value), and interaction (treatment by visit, treatment by subgroup).
Standardized effect size (d) = LS mean difference/estimated pooled standard deviation with the small sample bias correction.

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Table 12.3
Cardiac Biomarkers - NT-proBNP (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Age (years): <65

Subgroup Visit	Vutrisiran (HELIOS-A) (N=76)	Patisiran (HELIOS-A) (N=31)
Baseline		
n	76	31
Mean (SD)	811.588 (2357.143)	697.067 (1070.108)
SE	270.383	192.197
Geometric Mean (SEM)	171.357 (33.339)	205.758 (67.013)
CV (%) Geometric Mean	409.3	507.9
Median	147.702	236.542
Min, Max	4.99, 18755.00	4.99, 4200.25
Week 12		
Actual Value		
n	74	29
Mean (SD)	952.606 (3617.523)	542.353 (731.408)
SE	420.529	135.819
Geometric Mean (SEM)	171.480 (34.211)	154.896 (53.168)
CV (%) Geometric Mean	424.5	542.9
Median	129.223	104.782
Min, Max	4.99, 30496.62	4.99, 2250.32
Change from baseline		
n	74	29
Mean (SD)	127.390 (1411.702)	-39.369 (412.044)
SE	164.107	76.515
Median	-6.004	-29.938
Min, Max	-1699.43, 11741.61	-1200.47, 1348.13

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Table 12.3
Cardiac Biomarkers - NT-proBNP (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Age (years): <65

Subgroup Visit	Vutrisiran (HELIOS-A) (N=76)	Patisiran (HELIOS-A) (N=31)
Week 24		
Actual Value		
n	75	29
Mean (SD)	851.109 (2900.784)	707.209 (1300.529)
SE	334.954	241.502
Geometric Mean (SEM)	175.888 (33.972)	172.937 (59.502)
CV (%) Geometric Mean	392.6	547.5
Median	137.680	157.638
Min, Max	4.99, 24392.27	4.99, 5480.64
Change from baseline		
n	75	29
Mean (SD)	28.926 (756.902)	34.160 (422.672)
SE	87.400	78.488
Median	2.960	-8.034
Min, Max	-1970.90, 5637.27	-1187.53, 1280.39

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Table 12.3
Cardiac Biomarkers - NT-proBNP (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Age (years): <65

Subgroup Visit	Vutrisiran (HELIOS-A) (N=76)	Patisiran (HELIOS-A) (N=31)
Month 9		
Actual Value		
n	73	29
Mean (SD)	606.340 (1174.126)	957.948 (2076.130)
SE	137.421	385.528
Geometric Mean (SEM)	176.303 (31.879)	225.730 (75.186)
CV (%) Geometric Mean	314.3	489.5
Median	123.726	188.591
Min, Max	10.99, 7455.52	4.99, 10173.86
Change from baseline		
n	73	29
Mean (SD)	22.705 (393.841)	273.129 (1210.227)
SE	46.096	224.734
Median	5.920	12.009
Min, Max	-1712.46, 1647.59	-1179.50, 5973.60

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Table 12.3
Cardiac Biomarkers - NT-proBNP (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Age (years): <65

Subgroup Visit	Vutrisiran (HELIOS-A) (N=76)	Patisiran (HELIOS-A) (N=31)
Week 48		
Actual Value		
n	72	29
Mean (SD)	572.517 (1001.742)	738.054 (1343.264)
SE	118.056	249.438
Geometric Mean (SEM)	158.686 (30.667)	195.275 (63.801)
CV (%) Geometric Mean	370.4	459.4
Median	128.716	181.656
Min, Max	6.00, 5037.50	4.99, 5318.95
Change from baseline		
n	72	29
Mean (SD)	-8.885 (451.792)	65.005 (444.938)
SE	53.244	82.623
Median	-3.510	11.924
Min, Max	-2250.32, 1747.30	-724.43, 2112.64

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Table 12.3
Cardiac Biomarkers - NT-proBNP (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Age (years): <65

Subgroup Visit	Vutrisiran (HELIOS-A) (N=76)	Patisiran (HELIOS-A) (N=31)
Week 60		
Actual Value		
n	75	26
Mean (SD)	529.974 (968.464)	609.115 (1312.044)
SE	111.829	257.313
Geometric Mean (SEM)	152.657 (27.949)	178.163 (55.124)
CV (%) Geometric Mean	337.0	332.4
Median	108.757	115.734
Min, Max	10.99, 4783.03	10.99, 6561.36
Change from baseline		
n	75	26
Mean (SD)	-42.368 (468.242)	40.642 (570.642)
SE	54.068	111.912
Median	-3.975	-4.524
Min, Max	-2485.85, 1489.87	-1470.93, 2361.11

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Table 12.3
Cardiac Biomarkers - NT-proBNP (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Age (years): <65

Subgroup Visit	Vutrisiran (HELIOS-A) (N=76)	Patisiran (HELIOS-A) (N=31)
Week 72		
Actual Value		
n	75	28
Mean (SD)	608.456 (1282.630)	731.189 (1811.693)
SE	148.105	342.378
Geometric Mean (SEM)	149.464 (28.857)	161.046 (53.057)
CV (%) Geometric Mean	392.1	445.9
Median	124.741	147.659
Min, Max	4.99, 7395.65	4.99, 8937.44
Change from baseline		
n	75	28
Mean (SD)	36.114 (713.173)	134.037 (1152.096)
SE	82.350	217.726
Median	-6.004	-0.507
Min, Max	-1151.59, 5487.58	-1682.44, 5731.14

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Table 12.3
Cardiac Biomarkers - NT-proBNP (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Age (years): <65

Subgroup Visit	Vutrisiran (HELIOS-A) (N=76)	Patisiran (HELIOS-A) (N=31)
Month 18		
Actual Value		
n	74	29
Mean (SD)	677.917 (1560.380)	802.266 (1713.147)
SE	181.390	318.123
Geometric Mean (SEM)	146.183 (29.515)	182.103 (59.804)
CV (%) Geometric Mean	440.7	467.1
Median	106.304	125.756
Min, Max	4.99, 9582.12	4.99, 7947.47
Change from baseline		
n	74	29
Mean (SD)	114.859 (1002.211)	167.069 (1003.603)
SE	116.505	186.364
Median	-7.484	-4.990
Min, Max	-1725.40, 7674.05	-1911.03, 4741.16

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Table 12.3
Cardiac Biomarkers - NT-proBNP (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Age (years): ≥65

Subgroup Visit	Vutrisiran (HELIOS-A) (N=46)	Patisiran (HELIOS-A) (N=11)
Baseline		
n	46	11
Mean (SD)	1338.545 (1725.180)	2605.571 (4105.300)
SE	254.364	1237.795
Geometric Mean (SEM)	589.325 (125.518)	1074.537 (476.739)
CV (%) Geometric Mean	265.7	277.8
Median	705.060	1495.874
Min, Max	27.91, 7588.21	70.87, 14324.21
Week 12		
Actual Value		
n	44	9
Mean (SD)	1277.230 (1726.379)	2842.313 (5132.140)
SE	260.261	1710.713
Geometric Mean (SEM)	565.485 (123.984)	876.971 (470.563)
CV (%) Geometric Mean	270.0	351.4
Median	618.714	559.853
Min, Max	12.01, 7156.14	84.82, 15851.04
Change from baseline		
n	44	9
Mean (SD)	86.409 (664.178)	45.470 (709.363)
SE	100.129	236.454
Median	-10.487	13.954
Min, Max	-1201.49, 2803.16	-863.21, 1526.83

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Table 12.3
Cardiac Biomarkers - NT-proBNP (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Age (years): ≥65

Subgroup Visit	Vutrisiran (HELIOS-A) (N=46)	Patisiran (HELIOS-A) (N=11)
Week 24		
Actual Value		
n	43	9
Mean (SD)	1270.776 (1990.032)	2864.715 (4618.904)
SE	303.477	1539.635
Geometric Mean (SEM)	477.369 (115.605)	883.026 (493.175)
CV (%) Geometric Mean	338.4	394.5
Median	582.772	644.677
Min, Max	14.97, 9061.17	72.81, 13526.89
Change from baseline		
n	43	9
Mean (SD)	90.508 (804.092)	167.890 (1048.338)
SE	122.623	349.446
Median	-7.019	1.945
Min, Max	-953.02, 4519.59	-797.33, 2801.21

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Table 12.3
Cardiac Biomarkers - NT-proBNP (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Age (years): ≥65

Subgroup Visit	Vutrisiran (HELIOS-A) (N=46)	Patisiran (HELIOS-A) (N=11)
Month 9		
Actual Value		
n	40	9
Mean (SD)	1014.857 (1133.927)	2100.409 (4270.195)
SE	179.290	1423.398
Geometric Mean (SEM)	494.594 (111.501)	682.485 (331.530)
CV (%) Geometric Mean	257.6	271.3
Median	575.795	425.133
Min, Max	13.95, 4942.69	84.82, 13397.16
Change from baseline		
n	40	9
Mean (SD)	-156.833 (904.379)	728.937 (3018.150)
SE	142.995	1006.050
Median	-12.981	-44.907
Min, Max	-4190.27, 1722.44	-950.06, 8722.89

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Table 12.3
Cardiac Biomarkers - NT-proBNP (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Age (years): ≥65

Subgroup Visit	Vutrisiran (HELIOS-A) (N=46)	Patisiran (HELIOS-A) (N=11)
Week 48		
Actual Value		
n	42	10
Mean (SD)	1223.430 (1589.035)	3264.216 (5577.488)
SE	245.193	1763.757
Geometric Mean (SEM)	529.354 (124.778)	911.596 (477.395)
CV (%) Geometric Mean	305.2	381.1
Median	547.379	702.565
Min, Max	10.99, 7502.37	88.80, 15523.75
Change from baseline		
n	42	10
Mean (SD)	-13.880 (1256.956)	597.470 (2380.152)
SE	193.953	752.670
Median	-21.438	-57.846
Min, Max	-4292.10, 5112.34	-1159.62, 7155.13

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Table 12.3
Cardiac Biomarkers - NT-proBNP (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Age (years): ≥65

Subgroup Visit	Vutrisiran (HELIOS-A) (N=46)	Patisiran (HELIOS-A) (N=11)
Week 60		
Actual Value		
n	43	9
Mean (SD)	1019.249 (1210.756)	2065.049 (3945.431)
SE	184.639	1315.144
Geometric Mean (SEM)	499.573 (104.927)	762.942 (351.065)
CV (%) Geometric Mean	238.0	239.2
Median	532.876	643.662
Min, Max	9.98, 5021.60	94.80, 12454.12
Change from baseline		
n	43	9
Mean (SD)	-173.156 (854.449)	-378.639 (778.210)
SE	130.302	259.403
Median	4.990	-90.744
Min, Max	-4326.01, 1427.03	-1870.10, 450.08

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Table 12.3
Cardiac Biomarkers - NT-proBNP (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Age (years): ≥65

Subgroup Visit	Vutrisiran (HELIOS-A) (N=46)	Patisiran (HELIOS-A) (N=11)
Week 72		
Actual Value		
n	43	9
Mean (SD)	1223.923 (1847.832)	2189.771 (4372.327)
SE	281.792	1457.442
Geometric Mean (SEM)	507.794 (113.049)	764.843 (364.556)
CV (%) Geometric Mean	272.5	259.4
Median	485.009	653.642
Min, Max	15.98, 8107.13	76.87, 13774.34
Change from baseline		
n	43	9
Mean (SD)	169.417 (1455.176)	-253.917 (511.308)
SE	221.912	170.436
Median	8.964	-149.689
Min, Max	-4150.36, 5402.75	-1215.52, 343.27

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Table 12.3
Cardiac Biomarkers - NT-proBNP (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Age (years): ≥65

Subgroup Visit	Vutrisiran (HELIOS-A) (N=46)	Patisiran (HELIOS-A) (N=11)
Month 18		
Actual Value		
n	40	9
Mean (SD)	1139.156 (1335.474)	2323.617 (4795.149)
SE	211.157	1598.383
Geometric Mean (SEM)	513.395 (116.116)	812.614 (358.511)
CV (%) Geometric Mean	259.6	218.3
Median	490.464	804.345
Min, Max	26.98, 5501.53	202.55, 15039.76
Change from baseline		
n	40	9
Mean (SD)	49.522 (1106.422)	-120.071 (681.511)
SE	174.941	227.170
Median	2.495	-7.950
Min, Max	-4300.05, 3111.50	-1591.69, 715.55

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Table 12.3
Cardiac Biomarkers - NT-proBNP (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Sex: Male

Subgroup Visit	Vutrisiran (HELIOS-A) (N=79)	Patisiran (HELIOS-A) (N=27)
Baseline		
n	79	27
Mean (SD)	921.439 (1511.676)	1323.984 (2823.811)
SE	170.077	543.443
Geometric Mean (SEM)	288.169 (54.131)	311.994 (116.494)
CV (%) Geometric Mean	390.4	649.1
Median	303.353	427.079
Min, Max	9.98, 7588.21	4.99, 14324.21
Week 12		
Actual Value		
n	76	24
Mean (SD)	857.639 (1419.137)	1372.314 (3292.119)
SE	162.786	672.001
Geometric Mean (SEM)	263.827 (51.434)	248.039 (104.298)
CV (%) Geometric Mean	411.9	828.6
Median	333.290	289.864
Min, Max	7.02, 7156.14	4.99, 15851.04
Change from baseline		
n	76	24
Mean (SD)	28.323 (554.298)	50.689 (544.577)
SE	63.582	111.161
Median	-13.996	-1.015
Min, Max	-1699.43, 2803.16	-1200.47, 1526.83

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

Alnylam Pharmaceuticals Inc.
ALN-TTRSC02-002

Table 12.3
Cardiac Biomarkers - NT-proBNP (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Sex: Male

Subgroup Visit	Vutrisiran (HELIOS-A) (N=79)	Patisiran (HELIOS-A) (N=27)
Week 24		
Actual Value		
n	75	25
Mean (SD)	871.666 (1596.748)	1294.303 (2963.799)
SE	184.377	592.760
Geometric Mean (SEM)	262.043 (49.996)	249.165 (100.038)
CV (%) Geometric Mean	378.6	743.3
Median	322.296	297.348
Min, Max	17.00, 9061.17	4.99, 13526.89
Change from baseline		
n	75	25
Mean (SD)	45.597 (638.188)	-3.038 (667.547)
SE	73.692	133.509
Median	-7.019	-8.034
Min, Max	-1500.86, 4519.59	-1187.53, 2801.21

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

Alnylam Pharmaceuticals Inc.
ALN-TTRSC02-002

Table 12.3
Cardiac Biomarkers - NT-proBNP (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Sex: Male

Subgroup Visit	Vutrisiran (HELIOS-A) (N=79)	Patisiran (HELIOS-A) (N=27)
Month 9		
Actual Value		
n	73	24
Mean (SD)	798.526 (1257.105)	1045.497 (2690.890)
SE	147.133	549.276
Geometric Mean (SEM)	284.065 (51.518)	254.304 (91.340)
CV (%) Geometric Mean	316.8	459.5
Median	304.367	279.927
Min, Max	13.95, 7455.52	4.99, 13397.16
Change from baseline		
n	73	24
Mean (SD)	-14.332 (683.882)	290.942 (1828.287)
SE	80.042	373.198
Median	6.004	1.480
Min, Max	-4190.27, 1647.59	-1179.50, 8722.89

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

Alnylam Pharmaceuticals Inc.
ALN-TTRSC02-002

Table 12.3
Cardiac Biomarkers - NT-proBNP (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Sex: Male

Subgroup Visit	Vutrisiran (HELIOS-A) (N=79)	Patisiran (HELIOS-A) (N=27)
Week 48		
Actual Value		
n	75	25
Mean (SD)	844.030 (1373.849)	1531.739 (3745.768)
SE	158.638	749.154
Geometric Mean (SEM)	263.500 (51.308)	259.924 (101.210)
CV (%) Geometric Mean	402.2	657.9
Median	327.286	265.465
Min, Max	7.95, 7502.37	4.99, 15523.75
Change from baseline		
n	75	25
Mean (SD)	4.029 (911.358)	234.398 (1478.783)
SE	105.235	295.757
Median	-7.019	-14.969
Min, Max	-4292.10, 5112.34	-724.43, 7155.13

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

Alnylam Pharmaceuticals Inc.
ALN-TTRSC02-002

Table 12.3
Cardiac Biomarkers - NT-proBNP (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Sex: Male

Subgroup Visit	Vutrisiran (HELIOS-A) (N=79)	Patisiran (HELIOS-A) (N=27)
Week 60		
Actual Value		
n	77	22
Mean (SD)	740.381 (1117.780)	1022.148 (2616.116)
SE	127.383	557.758
Geometric Mean (SEM)	253.697 (46.577)	266.317 (92.332)
CV (%) Geometric Mean	352.2	361.6
Median	259.461	313.374
Min, Max	9.98, 5021.60	10.99, 12454.12
Change from baseline		
n	77	22
Mean (SD)	-85.811 (718.182)	-154.494 (548.521)
SE	81.844	116.945
Median	-4.990	-4.524
Min, Max	-4326.01, 1489.87	-1870.10, 450.08

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Alnylam Pharmaceuticals Inc.
ALN-TTRSC02-002

Table 12.3
Cardiac Biomarkers - NT-proBNP (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Sex: Male

Subgroup Visit	Vutrisiran (HELIOS-A) (N=79)	Patisiran (HELIOS-A) (N=27)
Week 72		
Actual Value		
n	76	23
Mean (SD)	807.349 (1435.939)	988.458 (2825.209)
SE	164.713	589.097
Geometric Mean (SEM)	251.295 (47.292)	215.860 (79.773)
CV (%) Geometric Mean	370.9	470.4
Median	263.478	329.316
Min, Max	6.00, 7395.65	4.99, 13774.34
Change from baseline		
n	76	23
Mean (SD)	63.080 (1035.807)	-137.242 (406.174)
SE	118.815	84.693
Median	4.990	0.000
Min, Max	-4150.36, 5487.58	-1682.44, 343.27

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Alnylam Pharmaceuticals Inc.
ALN-TTRSC02-002

Table 12.3
Cardiac Biomarkers - NT-proBNP (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Sex: Male

Subgroup Visit	Vutrisiran (HELIOS-A) (N=79)	Patisiran (HELIOS-A) (N=27)
Month 18		
Actual Value		
n	73	23
Mean (SD)	919.075 (1705.017)	1076.028 (3085.739)
SE	199.557	643.421
Geometric Mean (SEM)	241.744 (49.315)	222.529 (83.531)
CV (%) Geometric Mean	445.7	495.5
Median	241.532	252.441
Min, Max	10.99, 9582.12	4.99, 15039.76
Change from baseline		
n	73	23
Mean (SD)	177.236 (1224.555)	-49.672 (507.000)
SE	143.323	105.717
Median	0.000	-7.950
Min, Max	-4300.05, 7674.05	-1911.03, 947.01

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Alnylam Pharmaceuticals Inc.
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Table 12.3
Cardiac Biomarkers - NT-proBNP (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Sex: Female

Subgroup Visit	Vutrisiran (HELIOS-A) (N=43)	Patisiran (HELIOS-A) (N=15)
Baseline		
n	43	15
Mean (SD)	1173.489 (3002.323)	968.186 (1307.102)
SE	457.850	337.492
Geometric Mean (SEM)	247.196 (67.658)	326.867 (150.621)
CV (%) Geometric Mean	490.5	481.4
Median	222.504	348.259
Min, Max	4.99, 18755.00	7.95, 4200.25
Week 12		
Actual Value		
n	42	14
Mean (SD)	1464.533 (4750.782)	598.109 (756.882)
SE	733.062	202.285
Geometric Mean (SEM)	274.490 (75.000)	210.640 (97.765)
CV (%) Geometric Mean	469.1	440.5
Median	222.039	317.307
Min, Max	4.99, 30496.62	15.98, 2250.32
Change from baseline		
n	42	14
Mean (SD)	263.721 (1847.573)	-139.214 (360.447)
SE	285.087	96.333
Median	15.984	-64.865
Min, Max	-1260.35, 11741.61	-955.98, 239.50

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Alnylam Pharmaceuticals Inc.
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Table 12.3
Cardiac Biomarkers - NT-proBNP (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Sex: Female

Subgroup Visit	Vutrisiran (HELIOS-A) (N=43)	Patisiran (HELIOS-A) (N=15)
Week 24		
Actual Value		
n	43	13
Mean (SD)	1234.921 (3784.500)	1071.840 (1797.273)
SE	577.131	498.474
Geometric Mean (SEM)	238.161 (65.816)	264.911 (134.301)
CV (%) Geometric Mean	506.8	522.0
Median	200.600	202.545
Min, Max	4.99, 24392.27	27.91, 5480.64
Change from baseline		
n	43	13
Mean (SD)	61.431 (969.881)	198.278 (489.530)
SE	147.905	135.771
Median	3.975	-6.004
Min, Max	-1970.90, 5637.27	-226.56, 1280.39

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Table 12.3
Cardiac Biomarkers - NT-proBNP (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Sex: Female

Subgroup Visit	Vutrisiran (HELIOS-A) (N=43)	Patisiran (HELIOS-A) (N=15)
Month 9		
Actual Value		
n	40	14
Mean (SD)	664.118 (1005.958)	1542.303 (2866.348)
SE	159.056	766.064
Geometric Mean (SEM)	207.103 (53.259)	374.754 (182.033)
CV (%) Geometric Mean	361.8	511.9
Median	149.689	401.665
Min, Max	10.99, 3922.86	30.95, 10173.86
Change from baseline		
n	40	14
Mean (SD)	-89.240 (508.394)	535.612 (1707.475)
SE	80.384	456.342
Median	-6.004	17.506
Min, Max	-1712.46, 1722.44	-950.06, 5973.60

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Table 12.3
Cardiac Biomarkers - NT-proBNP (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Sex: Female

Subgroup Visit	Vutrisiran (HELIOS-A) (N=43)	Patisiran (HELIOS-A) (N=15)
Week 48		
Actual Value		
n	39	14
Mean (SD)	751.359 (1101.677)	1125.162 (1748.126)
SE	176.409	467.206
Geometric Mean (SEM)	219.004 (60.688)	352.233 (159.280)
CV (%) Geometric Mean	435.7	406.3
Median	158.653	350.796
Min, Max	6.00, 4001.68	33.91, 5318.95
Change from baseline		
n	39	14
Mean (SD)	-39.097 (683.647)	142.851 (683.829)
SE	109.471	182.761
Median	1.945	26.470
Min, Max	-2250.32, 2879.02	-1159.62, 2112.64

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Alnylam Pharmaceuticals Inc.
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Table 12.3
Cardiac Biomarkers - NT-proBNP (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Sex: Female

Subgroup Visit	Vutrisiran (HELIOS-A) (N=43)	Patisiran (HELIOS-A) (N=15)
Week 60		
Actual Value		
n	41	13
Mean (SD)	647.963 (1028.745)	918.092 (1777.783)
SE	160.663	493.068
Geometric Mean (SEM)	203.901 (51.739)	246.992 (118.708)
CV (%) Geometric Mean	360.7	437.5
Median	147.659	288.384
Min, Max	12.01, 4942.69	28.92, 6561.36
Change from baseline		
n	41	13
Mean (SD)	-97.949 (451.440)	80.602 (784.803)
SE	70.503	217.665
Median	0.930	-14.969
Min, Max	-2485.85, 426.06	-1281.32, 2361.11

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Table 12.3
Cardiac Biomarkers - NT-proBNP (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Sex: Female

Subgroup Visit	Vutrisiran (HELIOS-A) (N=43)	Patisiran (HELIOS-A) (N=15)
Week 72		
Actual Value		
n	42	14
Mean (SD)	878.676 (1715.920)	1246.193 (2478.680)
SE	264.772	662.455
Geometric Mean (SEM)	204.184 (57.007)	270.965 (135.318)
CV (%) Geometric Mean	504.1	564.2
Median	166.180	295.868
Min, Max	4.99, 8107.13	17.00, 8937.44
Change from baseline		
n	42	14
Mean (SD)	123.794 (1064.882)	330.312 (1603.419)
SE	164.315	428.532
Median	-11.502	-14.969
Min, Max	-1151.59, 5402.75	-1215.52, 5731.14

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Alnylam Pharmaceuticals Inc.
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Table 12.3
Cardiac Biomarkers - NT-proBNP (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Sex: Female

Subgroup Visit	Vutrisiran (HELIOS-A) (N=43)	Patisiran (HELIOS-A) (N=15)
Month 18		
Actual Value		
n	41	15
Mean (SD)	698.526 (1027.524)	1295.308 (2269.445)
SE	160.472	585.968
Geometric Mean (SEM)	203.320 (55.335)	328.512 (150.848)
CV (%) Geometric Mean	445.4	475.8
Median	219.544	325.341
Min, Max	4.99, 3448.85	41.95, 7947.47
Change from baseline		
n	41	15
Mean (SD)	-59.946 (541.597)	327.122 (1350.661)
SE	84.583	348.739
Median	-14.969	13.954
Min, Max	-1725.40, 1332.23	-1591.69, 4741.16

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Alnylam Pharmaceuticals Inc.
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Table 12.3
Cardiac Biomarkers - NT-proBNP (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Race: White

Subgroup Visit	Vutrisiran (HELIOS-A) (N=86)	Patisiran (HELIOS-A) (N=29)
Baseline		
n	86	29
Mean (SD)	699.059 (1294.346)	928.894 (1154.312)
SE	139.573	214.350
Geometric Mean (SEM)	226.270 (38.281)	306.806 (104.182)
CV (%) Geometric Mean	327.5	522.8
Median	219.036	330.330
Min, Max	9.98, 7588.21	4.99, 4200.25
Week 12		
Actual Value		
n	82	25
Mean (SD)	658.730 (1161.933)	582.346 (722.188)
SE	128.314	144.438
Geometric Mean (SEM)	217.292 (38.407)	195.715 (68.740)
CV (%) Geometric Mean	345.8	456.6
Median	206.562	177.597
Min, Max	4.99, 6818.79	4.99, 2250.32
Change from baseline		
n	82	25
Mean (SD)	44.982 (411.776)	-166.018 (376.315)
SE	45.473	75.263
Median	0.000	-39.917
Min, Max	-1201.49, 2803.16	-1200.47, 262.42

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Alnylam Pharmaceuticals Inc.
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Table 12.3
Cardiac Biomarkers - NT-proBNP (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Race: White

Subgroup Visit	Vutrisiran (HELIOS-A) (N=86)	Patisiran (HELIOS-A) (N=29)
Week 24		
Actual Value		
n	83	27
Mean (SD)	593.406 (1095.664)	833.741 (1344.389)
SE	120.265	258.728
Geometric Mean (SEM)	205.434 (35.174)	245.056 (82.969)
CV (%) Geometric Mean	322.4	459.2
Median	239.502	293.373
Min, Max	4.99, 8382.58	4.99, 5480.64
Change from baseline		
n	83	27
Mean (SD)	-20.149 (370.666)	-1.372 (452.913)
SE	40.686	87.163
Median	-2.960	-6.004
Min, Max	-1970.90, 1491.90	-1187.53, 1280.39

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Alnylam Pharmaceuticals Inc.
ALN-TTRSC02-002

Table 12.3
Cardiac Biomarkers - NT-proBNP (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Race: White

Subgroup Visit	Vutrisiran (HELIOS-A) (N=86)	Patisiran (HELIOS-A) (N=29)
Month 9		
Actual Value		
n	80	27
Mean (SD)	644.181 (996.263)	1097.762 (2131.956)
SE	111.386	410.295
Geometric Mean (SEM)	223.057 (38.198)	294.993 (102.307)
CV (%) Geometric Mean	307.3	497.3
Median	218.064	339.295
Min, Max	10.99, 4942.69	4.99, 10173.86
Change from baseline		
n	80	27
Mean (SD)	34.373 (484.574)	189.800 (1286.171)
SE	54.177	247.524
Median	6.977	0.000
Min, Max	-2109.68, 1722.44	-1179.50, 5973.60

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Alnylam Pharmaceuticals Inc.
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Table 12.3
Cardiac Biomarkers - NT-proBNP (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Race: White

Subgroup Visit	Vutrisiran (HELIOS-A) (N=86)	Patisiran (HELIOS-A) (N=29)
Week 48		
Actual Value		
n	79	28
Mean (SD)	744.363 (1307.215)	861.820 (1356.534)
SE	147.073	256.361
Geometric Mean (SEM)	217.666 (41.046)	276.101 (88.683)
CV (%) Geometric Mean	394.9	412.0
Median	199.585	301.365
Min, Max	6.00, 7502.37	4.99, 5318.95
Change from baseline		
n	79	28
Mean (SD)	118.437 (781.463)	-29.041 (523.874)
SE	87.922	99.003
Median	-3.045	-11.459
Min, Max	-2250.32, 5112.34	-1159.62, 2112.64

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Table 12.3
Cardiac Biomarkers - NT-proBNP (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Race: White

Subgroup Visit	Vutrisiran (HELIOS-A) (N=86)	Patisiran (HELIOS-A) (N=29)
Week 60		
Actual Value		
n	83	24
Mean (SD)	570.702 (904.906)	786.402 (1378.501)
SE	99.326	281.385
Geometric Mean (SEM)	199.977 (34.030)	283.846 (86.377)
CV (%) Geometric Mean	317.2	286.9
Median	197.556	313.374
Min, Max	9.98, 5021.60	28.92, 6561.36
Change from baseline		
n	83	24
Mean (SD)	-29.532 (469.718)	-23.412 (674.374)
SE	51.558	137.656
Median	-2.030	-0.507
Min, Max	-2485.85, 1489.87	-1470.93, 2361.11

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Table 12.3
Cardiac Biomarkers - NT-proBNP (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Race: White

Subgroup Visit	Vutrisiran (HELIOS-A) (N=86)	Patisiran (HELIOS-A) (N=29)
Week 72		
Actual Value		
n	83	26
Mean (SD)	730.998 (1444.088)	896.637 (1866.960)
SE	158.509	366.141
Geometric Mean (SEM)	201.441 (36.713)	228.418 (80.191)
CV (%) Geometric Mean	384.1	486.3
Median	177.597	329.823
Min, Max	4.99, 7395.65	4.99, 8937.44
Change from baseline		
n	83	26
Mean (SD)	202.206 (1039.130)	74.503 (1233.789)
SE	114.059	241.966
Median	5.920	-11.502
Min, Max	-1111.67, 5487.58	-1682.44, 5731.14

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Table 12.3
Cardiac Biomarkers - NT-proBNP (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Race: White

Subgroup Visit	Vutrisiran (HELIOS-A) (N=86)	Patisiran (HELIOS-A) (N=29)
Month 18		
Actual Value		
n	81	27
Mean (SD)	745.932 (1453.784)	936.240 (1750.023)
SE	161.532	336.792
Geometric Mean (SEM)	199.092 (37.594)	271.492 (89.507)
CV (%) Geometric Mean	411.8	422.1
Median	209.564	329.316
Min, Max	4.99, 9582.12	4.99, 7947.47
Change from baseline		
n	81	27
Mean (SD)	225.559 (1063.175)	81.576 (1085.088)
SE	118.131	208.825
Median	2.960	-7.950
Min, Max	-1725.40, 7674.05	-1911.03, 4741.16

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Table 12.3
Cardiac Biomarkers - NT-proBNP (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Race: All Other Races

Subgroup Visit	Vutrisiran (HELIOS-A) (N=36)	Patisiran (HELIOS-A) (N=13)
Baseline		
n	36	13
Mean (SD)	1753.742 (3329.376)	1794.803 (3962.565)
SE	554.896	1099.018
Geometric Mean (SEM)	427.534 (139.357)	341.763 (191.050)
CV (%) Geometric Mean	669.5	755.7
Median	592.244	427.079
Min, Max	4.99, 18755.00	7.02, 14324.21
Week 12		
Actual Value		
n	36	13
Mean (SD)	2018.752 (5156.818)	2057.725 (4386.420)
SE	859.470	1216.574
Geometric Mean (SEM)	429.885 (135.992)	328.065 (204.715)
CV (%) Geometric Mean	597.5	1252.6
Median	453.549	399.170
Min, Max	7.02, 30496.62	4.99, 15851.04
Change from baseline		
n	36	13
Mean (SD)	265.009 (2067.099)	262.922 (566.902)
SE	344.517	157.230
Median	-14.461	1.015
Min, Max	-1699.43, 11741.61	-371.26, 1526.83

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Table 12.3
Cardiac Biomarkers - NT-proBNP (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Race: All Other Races

Subgroup Visit	Vutrisiran (HELIOS-A) (N=36)	Patisiran (HELIOS-A) (N=13)
Week 24		
Actual Value		
n	35	11
Mean (SD)	1977.824 (4366.300)	2161.863 (4350.009)
SE	738.039	1311.577
Geometric Mean (SEM)	414.997 (136.378)	279.038 (199.525)
CV (%) Geometric Mean	654.3	1661.5
Median	502.938	311.387
Min, Max	14.97, 24392.27	7.95, 13526.89
Change from baseline		
n	35	11
Mean (SD)	220.962 (1294.292)	230.792 (903.467)
SE	218.775	272.405
Median	0.000	-8.034
Min, Max	-1500.86, 5637.27	-797.33, 2801.21

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Alnylam Pharmaceuticals Inc.
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Table 12.3
Cardiac Biomarkers - NT-proBNP (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Race: All Other Races

Subgroup Visit	Vutrisiran (HELIOS-A) (N=36)	Patisiran (HELIOS-A) (N=13)
Month 9		
Actual Value		
n	33	11
Mean (SD)	1009.776 (1501.896)	1549.507 (3946.632)
SE	261.447	1189.954
Geometric Mean (SEM)	348.040 (100.848)	289.371 (153.727)
CV (%) Geometric Mean	386.9	461.5
Median	378.197	303.353
Min, Max	17.93, 7455.52	21.99, 13397.16
Change from baseline		
n	33	11
Mean (SD)	-223.203 (862.390)	850.597 (2624.655)
SE	150.123	791.363
Median	-20.973	40.847
Min, Max	-4190.27, 1008.92	-392.24, 8722.89

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Table 12.3
Cardiac Biomarkers - NT-proBNP (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Race: All Other Races

Subgroup Visit	Vutrisiran (HELIOS-A) (N=36)	Patisiran (HELIOS-A) (N=13)
Week 48		
Actual Value		
n	35	11
Mean (SD)	965.731 (1231.176)	2719.525 (5486.438)
SE	208.107	1654.223
Geometric Mean (SEM)	330.056 (96.528)	328.155 (222.973)
CV (%) Geometric Mean	435.4	1263.1
Median	367.203	272.400
Min, Max	7.95, 5037.50	12.94, 15523.75
Change from baseline		
n	35	11
Mean (SD)	-302.260 (896.796)	788.454 (2143.587)
SE	151.586	646.316
Median	-9.049	26.978
Min, Max	-4292.10, 924.10	-154.68, 7155.13

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Table 12.3
Cardiac Biomarkers - NT-proBNP (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Race: All Other Races

Subgroup Visit	Vutrisiran (HELIOS-A) (N=36)	Patisiran (HELIOS-A) (N=13)
Week 60		
Actual Value		
n	35	11
Mean (SD)	1034.501 (1383.475)	1413.526 (3675.150)
SE	233.850	1108.100
Geometric Mean (SEM)	345.305 (99.946)	211.999 (127.606)
CV (%) Geometric Mean	421.5	726.7
Median	414.139	288.384
Min, Max	12.01, 4942.69	10.99, 12454.12
Change from baseline		
n	35	11
Mean (SD)	-233.491 (911.356)	-162.651 (596.223)
SE	154.047	179.768
Median	-3.975	-16.914
Min, Max	-4326.01, 1385.17	-1870.10, 341.24

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Table 12.3
Cardiac Biomarkers - NT-proBNP (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Race: All Other Races

Subgroup Visit	Vutrisiran (HELIOS-A) (N=36)	Patisiran (HELIOS-A) (N=13)
Week 72		
Actual Value		
n	35	11
Mean (SD)	1074.003 (1728.676)	1533.515 (4071.537)
SE	292.200	1227.615
Geometric Mean (SEM)	330.925 (98.364)	252.231 (141.780)
CV (%) Geometric Mean	458.6	559.6
Median	334.305	277.390
Min, Max	6.00, 8107.13	7.95, 13774.34
Change from baseline		
n	35	11
Mean (SD)	-193.989 (1009.552)	-42.662 (281.488)
SE	170.645	84.872
Median	-33.913	0.930
Min, Max	-4150.36, 3590.50	-549.87, 521.88

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Table 12.3
Cardiac Biomarkers - NT-proBNP (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Race: All Other Races

Subgroup Visit	Vutrisiran (HELIOS-A) (N=36)	Patisiran (HELIOS-A) (N=13)
Month 18		
Actual Value		
n	33	11
Mean (SD)	1070.046 (1593.710)	1718.163 (4445.396)
SE	277.429	1340.337
Geometric Mean (SEM)	313.964 (99.035)	232.308 (140.894)
CV (%) Geometric Mean	506.6	749.5
Median	273.415	252.441
Min, Max	10.99, 7684.03	17.00, 15039.76
Change from baseline		
n	33	11
Mean (SD)	-236.055 (897.095)	141.985 (429.268)
SE	156.164	129.429
Median	-28.923	-4.990
Min, Max	-4300.05, 1237.43	-425.13, 947.01

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Table 12.3
Cardiac Biomarkers - NT-proBNP (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Region: North America

Subgroup Visit	Vutrisiran (HELIOS-A) (N=27)	Patisiran (HELIOS-A) (N=8)
Baseline		
n	27	8
Mean (SD)	695.735 (1477.114)	2761.633 (4925.376)
SE	284.271	1741.383
Geometric Mean (SEM)	176.646 (58.104)	526.084 (406.336)
CV (%) Geometric Mean	419.1	1082.7
Median	197.556	577.317
Min, Max	17.00, 7052.38	29.94, 14324.21
Week 12		
Actual Value		
n	27	8
Mean (SD)	616.424 (1377.322)	3058.389 (5468.580)
SE	265.066	1933.435
Geometric Mean (SEM)	152.834 (51.001)	388.857 (360.851)
CV (%) Geometric Mean	438.4	3131.4
Median	136.750	643.155
Min, Max	4.99, 6818.79	15.98, 15851.04
Change from baseline		
n	27	8
Mean (SD)	-79.311 (205.017)	296.756 (551.857)
SE	39.456	195.111
Median	-22.918	112.774
Min, Max	-792.42, 452.11	-130.75, 1526.83

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Table 12.3
Cardiac Biomarkers - NT-proBNP (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Region: North America

Subgroup Visit	Vutrisiran (HELIOS-A) (N=27)	Patisiran (HELIOS-A) (N=8)
Week 24		
Actual Value		
n	26	8
Mean (SD)	691.870 (1683.387)	2973.566 (4949.719)
SE	330.139	1749.990
Geometric Mean (SEM)	153.476 (53.130)	487.221 (396.184)
CV (%) Geometric Mean	464.2	1404.6
Median	146.222	479.977
Min, Max	4.99, 8382.58	33.91, 13526.89
Change from baseline		
n	26	8
Mean (SD)	-29.970 (334.919)	211.932 (1078.919)
SE	65.683	381.456
Median	-8.922	-55.858
Min, Max	-851.28, 1330.20	-797.33, 2801.21

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Table 12.3
Cardiac Biomarkers - NT-proBNP (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Region: North America

Subgroup Visit	Vutrisiran (HELIOS-A) (N=27)	Patisiran (HELIOS-A) (N=8)
Month 9		
Actual Value		
n	23	7
Mean (SD)	468.930 (1035.588)	2351.698 (4915.804)
SE	215.935	1857.999
Geometric Mean (SEM)	142.628 (45.192)	344.606 (283.509)
CV (%) Geometric Mean	301.1	1063.9
Median	132.690	162.628
Min, Max	13.95, 4942.69	36.96, 13397.16
Change from baseline		
n	23	7
Mean (SD)	-141.967 (441.740)	1241.862 (3299.999)
SE	92.109	1247.282
Median	-13.954	-1.015
Min, Max	-2109.68, 92.86	-147.66, 8722.89

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Table 12.3
Cardiac Biomarkers - NT-proBNP (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Region: North America

Subgroup Visit	Vutrisiran (HELIOS-A) (N=27)	Patisiran (HELIOS-A) (N=8)
Week 48		
Actual Value		
n	26	8
Mean (SD)	541.648 (1198.184)	3794.867 (6202.112)
SE	234.983	2192.778
Geometric Mean (SEM)	125.441 (44.743)	667.122 (516.417)
CV (%) Geometric Mean	513.1	1094.3
Median	107.784	493.466
Min, Max	6.00, 5949.67	41.95, 15523.75
Change from baseline		
n	26	8
Mean (SD)	-179.773 (394.121)	1033.234 (2511.647)
SE	77.293	888.001
Median	-53.829	24.441
Min, Max	-1729.46, 121.78	-203.64, 7155.13

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Table 12.3
Cardiac Biomarkers - NT-proBNP (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Region: North America

Subgroup Visit	Vutrisiran (HELIOS-A) (N=27)	Patisiran (HELIOS-A) (N=8)
Week 60		
Actual Value		
n	27	7
Mean (SD)	534.733 (1041.404)	2242.470 (4550.816)
SE	200.418	1720.047
Geometric Mean (SEM)	154.047 (49.908)	345.099 (291.971)
CV (%) Geometric Mean	400.2	1220.6
Median	167.618	253.456
Min, Max	9.98, 5021.60	28.92, 12454.12
Change from baseline		
n	27	7
Mean (SD)	-161.002 (499.022)	-245.930 (718.825)
SE	96.037	271.690
Median	-30.953	-1.015
Min, Max	-2030.78, 309.36	-1870.10, 115.69

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Table 12.3
Cardiac Biomarkers - NT-proBNP (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Region: North America

Subgroup Visit	Vutrisiran (HELIOS-A) (N=27)	Patisiran (HELIOS-A) (N=8)
Week 72		
Actual Value		
n	26	6
Mean (SD)	406.736 (697.528)	2511.616 (5524.907)
SE	136.797	2255.534
Geometric Mean (SEM)	107.625 (37.483)	239.688 (241.245)
CV (%) Geometric Mean	473.5	2086.3
Median	89.813	248.509
Min, Max	4.99, 2806.20	17.00, 13774.34
Change from baseline		
n	26	6
Mean (SD)	-44.513 (283.135)	-108.109 (237.811)
SE	55.527	97.086
Median	-16.407	-50.361
Min, Max	-868.20, 784.39	-549.87, 150.70

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Table 12.3
Cardiac Biomarkers - NT-proBNP (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Region: North America

Subgroup Visit	Vutrisiran (HELIOS-A) (N=27)	Patisiran (HELIOS-A) (N=8)
Month 18		
Actual Value		
n	25	7
Mean (SD)	429.622 (872.658)	2642.643 (5524.207)
SE	174.532	2087.954
Geometric Mean (SEM)	117.618 (37.981)	420.186 (327.958)
CV (%) Geometric Mean	354.4	837.4
Median	98.778	187.576
Min, Max	12.01, 3880.92	43.89, 15039.76
Change from baseline		
n	25	7
Mean (SD)	-15.368 (517.288)	154.244 (345.151)
SE	103.458	130.455
Median	-23.933	13.954
Min, Max	-1256.46, 2123.55	-164.66, 715.55

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Table 12.3
Cardiac Biomarkers - NT-proBNP (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Region: Western Europe

Subgroup Visit	Vutrisiran (HELIOS-A) (N=42)	Patisiran (HELIOS-A) (N=20)
Baseline		
n	42	20
Mean (SD)	623.204 (1292.572)	786.860 (935.304)
SE	199.448	209.140
Geometric Mean (SEM)	183.947 (44.547)	264.895 (110.962)
CV (%) Geometric Mean	327.8	569.5
Median	111.802	306.862
Min, Max	9.98, 7588.21	4.99, 3206.30
Week 12		
Actual Value		
n	38	17
Mean (SD)	382.316 (536.736)	525.205 (672.824)
SE	87.070	163.184
Geometric Mean (SEM)	159.997 (36.936)	188.096 (77.846)
CV (%) Geometric Mean	256.5	417.0
Median	154.679	177.597
Min, Max	7.02, 2213.37	4.99, 2250.32
Change from baseline		
n	38	17
Mean (SD)	-48.812 (265.128)	-163.538 (357.516)
SE	43.009	86.710
Median	-6.004	-38.902
Min, Max	-1201.49, 446.11	-955.98, 218.61

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Table 12.3
Cardiac Biomarkers - NT-proBNP (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Region: Western Europe

Subgroup Visit	Vutrisiran (HELIOS-A) (N=42)	Patisiran (HELIOS-A) (N=20)
Week 24		
Actual Value		
n	39	16
Mean (SD)	338.193 (506.559)	631.928 (1133.517)
SE	81.114	283.379
Geometric Mean (SEM)	144.872 (32.169)	175.945 (78.669)
CV (%) Geometric Mean	241.7	484.8
Median	123.726	208.550
Min, Max	4.99, 2359.08	4.99, 4438.74
Change from baseline		
n	39	16
Mean (SD)	-55.476 (223.678)	53.385 (369.326)
SE	35.817	92.332
Median	6.935	7.950
Min, Max	-953.02, 433.08	-647.64, 1232.44

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Table 12.3
Cardiac Biomarkers - NT-proBNP (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Region: Western Europe

Subgroup Visit	Vutrisiran (HELIOS-A) (N=42)	Patisiran (HELIOS-A) (N=20)
Month 9		
Actual Value		
n	38	18
Mean (SD)	390.159 (533.600)	707.809 (1272.900)
SE	86.561	300.025
Geometric Mean (SEM)	159.736 (36.403)	227.126 (91.841)
CV (%) Geometric Mean	248.9	424.0
Median	118.736	297.898
Min, Max	10.99, 2085.67	4.99, 5444.70
Change from baseline		
n	38	18
Mean (SD)	-27.815 (259.283)	17.633 (634.443)
SE	42.061	149.540
Median	10.487	1.480
Min, Max	-1226.43, 528.90	-950.06, 2238.40

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Table 12.3
Cardiac Biomarkers - NT-proBNP (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Region: Western Europe

Subgroup Visit	Vutrisiran (HELIOS-A) (N=42)	Patisiran (HELIOS-A) (N=20)
Week 48		
Actual Value		
n	37	17
Mean (SD)	474.493 (714.918)	661.447 (1288.453)
SE	117.532	312.496
Geometric Mean (SEM)	184.237 (43.529)	183.968 (78.070)
CV (%) Geometric Mean	262.5	451.2
Median	158.653	230.538
Min, Max	14.97, 3283.18	4.99, 5318.95
Change from baseline		
n	37	17
Mean (SD)	42.555 (226.426)	-24.008 (633.280)
SE	37.224	153.593
Median	9.979	-14.969
Min, Max	-683.58, 875.21	-1159.62, 2112.64

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Table 12.3
Cardiac Biomarkers - NT-proBNP (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Region: Western Europe

Subgroup Visit	Vutrisiran (HELIOS-A) (N=42)	Patisiran (HELIOS-A) (N=20)
Week 60		
Actual Value		
n	40	16
Mean (SD)	361.266 (535.289)	460.415 (562.946)
SE	84.637	140.736
Geometric Mean (SEM)	159.534 (33.308)	243.515 (73.108)
CV (%) Geometric Mean	217.2	179.7
Median	148.167	313.374
Min, Max	10.99, 2384.03	36.96, 2169.47
Change from baseline		
n	40	16
Mean (SD)	-63.675 (224.992)	-115.327 (415.800)
SE	35.574	103.950
Median	0.507	11.967
Min, Max	-928.07, 137.76	-1281.32, 450.08

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Table 12.3
Cardiac Biomarkers - NT-proBNP (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Region: Western Europe

Subgroup Visit	Vutrisiran (HELIOS-A) (N=42)	Patisiran (HELIOS-A) (N=20)
Week 72		
Actual Value		
n	40	18
Mean (SD)	395.253 (591.893)	885.875 (2063.724)
SE	93.587	486.424
Geometric Mean (SEM)	164.081 (35.704)	214.387 (90.245)
CV (%) Geometric Mean	237.6	482.5
Median	159.161	331.303
Min, Max	14.97, 2200.43	4.99, 8937.44
Change from baseline		
n	40	18
Mean (SD)	-29.688 (278.440)	195.700 (1429.940)
SE	44.025	337.040
Median	6.004	3.002
Min, Max	-1111.67, 773.39	-1215.52, 5731.14

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Table 12.3
Cardiac Biomarkers - NT-proBNP (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Region: Western Europe

Subgroup Visit	Vutrisiran (HELIOS-A) (N=42)	Patisiran (HELIOS-A) (N=20)
Month 18		
Actual Value		
n	39	18
Mean (SD)	429.058 (719.161)	847.246 (1833.562)
SE	115.158	432.175
Geometric Mean (SEM)	157.292 (37.901)	229.445 (95.846)
CV (%) Geometric Mean	293.7	470.4
Median	142.670	337.307
Min, Max	4.99, 3035.72	4.99, 7947.47
Change from baseline		
n	39	18
Mean (SD)	5.530 (353.682)	157.070 (1228.736)
SE	56.634	289.616
Median	0.000	-6.004
Min, Max	-1031.84, 1332.23	-1591.69, 4741.16

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Table 12.3
Cardiac Biomarkers - NT-proBNP (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Region: Rest of World

Subgroup Visit	Vutrisiran (HELIOS-A) (N=53)	Patisiran (HELIOS-A) (N=14)
Baseline		
n	53	14
Mean (SD)	1477.251 (2817.689)	888.577 (1293.312)
SE	387.039	345.652
Geometric Mean (SEM)	465.990 (108.577)	307.387 (143.536)
CV (%) Geometric Mean	409.5	449.1
Median	492.959	428.093
Min, Max	4.99, 18755.00	7.02, 4200.25
Week 12		
Actual Value		
n	53	13
Mean (SD)	1802.254 (4328.913)	608.728 (707.787)
SE	594.622	196.305
Geometric Mean (SEM)	514.605 (120.436)	226.476 (113.733)
CV (%) Geometric Mean	415.1	505.3
Median	702.523	352.234
Min, Max	7.02, 30496.62	4.99, 2010.82
Change from baseline		
n	53	13
Mean (SD)	325.003 (1734.424)	-25.104 (539.960)
SE	238.241	149.758
Median	9.979	-43.892
Min, Max	-1699.43, 11741.61	-1200.47, 1348.13

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Table 12.3
Cardiac Biomarkers - NT-proBNP (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Region: Rest of World

Subgroup Visit	Vutrisiran (HELIOS-A) (N=53)	Patisiran (HELIOS-A) (N=14)
Week 24		
Actual Value		
n	53	14
Mean (SD)	1647.140 (3593.477)	885.152 (1455.238)
SE	493.602	388.929
Geometric Mean (SEM)	487.611 (112.922)	267.593 (134.889)
CV (%) Geometric Mean	402.0	583.7
Median	582.772	321.831
Min, Max	22.92, 24392.27	7.95, 5480.64
Change from baseline		
n	53	14
Mean (SD)	169.888 (1105.813)	-3.425 (517.559)
SE	151.895	138.323
Median	-2.030	-19.959
Min, Max	-1970.90, 5637.27	-1187.53, 1280.39

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Table 12.3
Cardiac Biomarkers - NT-proBNP (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Region: Rest of World

Subgroup Visit	Vutrisiran (HELIOS-A) (N=53)	Patisiran (HELIOS-A) (N=14)
Month 9		
Actual Value		
n	52	13
Mean (SD)	1139.340 (1434.634)	1344.748 (2725.006)
SE	198.948	755.781
Geometric Mean (SEM)	460.154 (98.131)	383.358 (180.887)
CV (%) Geometric Mean	310.5	413.2
Median	545.857	426.148
Min, Max	18.94, 7455.52	21.99, 10173.86
Change from baseline		
n	52	13
Mean (SD)	-5.647 (849.598)	420.827 (1721.033)
SE	117.818	477.329
Median	16.956	40.847
Min, Max	-4190.27, 1722.44	-1179.50, 5973.60

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Table 12.3
Cardiac Biomarkers - NT-proBNP (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Region: Rest of World

Subgroup Visit	Vutrisiran (HELIOS-A) (N=53)	Patisiran (HELIOS-A) (N=14)
Week 48		
Actual Value		
n	51	14
Mean (SD)	1195.415 (1536.941)	888.728 (1339.251)
SE	215.215	357.930
Geometric Mean (SEM)	432.939 (100.305)	312.735 (141.621)
CV (%) Geometric Mean	380.1	408.1
Median	438.073	350.796
Min, Max	12.01, 7502.37	12.94, 4828.95
Change from baseline		
n	51	14
Mean (SD)	36.803 (1204.809)	0.151 (290.337)
SE	168.707	77.596
Median	1.945	1.987
Min, Max	-4292.10, 5112.34	-724.43, 628.69

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Table 12.3
Cardiac Biomarkers - NT-proBNP (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Region: Rest of World

Subgroup Visit	Vutrisiran (HELIOS-A) (N=53)	Patisiran (HELIOS-A) (N=14)
Week 60		
Actual Value		
n	51	12
Mean (SD)	1072.301 (1309.637)	946.543 (1839.897)
SE	183.386	531.133
Geometric Mean (SEM)	398.785 (92.554)	237.758 (129.555)
CV (%) Geometric Mean	382.1	585.4
Median	554.864	312.359
Min, Max	12.01, 4942.69	10.99, 6561.36
Change from baseline		
n	51	12
Mean (SD)	-73.123 (880.095)	101.308 (845.630)
SE	123.238	244.112
Median	0.930	-14.927
Min, Max	-4326.01, 1489.87	-1470.93, 2361.11

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Table 12.3
Cardiac Biomarkers - NT-proBNP (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Region: Rest of World

Subgroup Visit	Vutrisiran (HELIOS-A) (N=53)	Patisiran (HELIOS-A) (N=14)
Week 72		
Actual Value		
n	52	13
Mean (SD)	1382.262 (2084.478)	705.060 (1162.648)
SE	289.065	322.461
Geometric Mean (SEM)	450.713 (104.110)	265.241 (116.293)
CV (%) Geometric Mean	387.7	334.2
Median	549.832	277.390
Min, Max	15.98, 8107.13	7.95, 4286.09
Change from baseline		
n	52	13
Mean (SD)	237.276 (1533.061)	-108.165 (504.798)
SE	212.597	140.006
Median	5.962	0.930
Min, Max	-4150.36, 5487.58	-1682.44, 521.88

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Table 12.3
Cardiac Biomarkers - NT-proBNP (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Region: Rest of World

Subgroup Visit	Vutrisiran (HELIOS-A) (N=53)	Patisiran (HELIOS-A) (N=14)
Month 18		
Actual Value		
n	50	13
Mean (SD)	1365.164 (1970.719)	802.257 (1383.084)
SE	278.702	383.598
Geometric Mean (SEM)	420.473 (106.548)	237.425 (114.009)
CV (%) Geometric Mean	487.8	436.3
Median	550.382	252.441
Min, Max	10.99, 9582.12	17.00, 5066.50
Change from baseline		
n	50	13
Mean (SD)	212.979 (1489.346)	-10.968 (699.021)
SE	210.625	193.874
Median	-0.507	-7.950
Min, Max	-4300.05, 7674.05	-1911.03, 947.01

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Table 12.3
Cardiac Biomarkers - NT-proBNP (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Baseline NIS: <50

Subgroup Visit	Vutrisiran (HELIOS-A) (N=78)	Patisiran (HELIOS-A) (N=27)
Baseline		
n	78	27
Mean (SD)	858.508 (2371.446)	1161.989 (2847.756)
SE	268.513	548.051
Geometric Mean (SEM)	184.502 (35.279)	204.726 (79.113)
CV (%) Geometric Mean	404.0	744.1
Median	153.664	183.601
Min, Max	4.99, 18755.00	4.99, 14324.21
Week 12		
Actual Value		
n	77	25
Mean (SD)	990.516 (3587.956)	1240.097 (3263.465)
SE	408.886	652.693
Geometric Mean (SEM)	185.345 (36.710)	151.495 (64.899)
CV (%) Geometric Mean	441.6	986.4
Median	145.714	87.784
Min, Max	4.99, 30496.62	4.99, 15851.04
Change from baseline		
n	77	25
Mean (SD)	121.195 (1360.656)	66.540 (496.136)
SE	155.061	99.227
Median	-8.034	-29.938
Min, Max	-1201.49, 11741.61	-955.98, 1526.83

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Table 12.3
Cardiac Biomarkers - NT-proBNP (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Baseline NIS: <50

Subgroup Visit	Vutrisiran (HELIOS-A) (N=78)	Patisiran (HELIOS-A) (N=27)
Week 24		
Actual Value		
n	76	27
Mean (SD)	879.486 (2967.259)	1271.645 (2939.654)
SE	340.368	565.737
Geometric Mean (SEM)	173.230 (33.658)	191.531 (76.685)
CV (%) Geometric Mean	407.7	864.9
Median	129.730	157.638
Min, Max	4.99, 24392.27	4.99, 13526.89
Change from baseline		
n	76	27
Mean (SD)	20.248 (736.146)	109.656 (620.095)
SE	84.442	119.337
Median	-3.467	-6.004
Min, Max	-1970.90, 5637.27	-797.33, 2801.21

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Table 12.3
Cardiac Biomarkers - NT-proBNP (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Baseline NIS: <50

Subgroup Visit	Vutrisiran (HELIOS-A) (N=78)	Patisiran (HELIOS-A) (N=27)
Month 9		
Actual Value		
n	74	25
Mean (SD)	532.306 (946.470)	1116.886 (2797.277)
SE	110.025	559.455
Geometric Mean (SEM)	164.975 (29.260)	202.770 (76.136)
CV (%) Geometric Mean	304.2	573.9
Median	128.250	162.628
Min, Max	10.99, 4942.69	4.99, 13397.16
Change from baseline		
n	74	25
Mean (SD)	-61.578 (408.335)	452.071 (1788.768)
SE	47.468	357.754
Median	-6.004	2.960
Min, Max	-2109.68, 1722.44	-518.92, 8722.89

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Table 12.3
Cardiac Biomarkers - NT-proBNP (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Baseline NIS: <50

Subgroup Visit	Vutrisiran (HELIOS-A) (N=78)	Patisiran (HELIOS-A) (N=27)
Week 48		
Actual Value		
n	74	27
Mean (SD)	599.024 (1069.355)	1512.227 (3697.242)
SE	124.310	711.535
Geometric Mean (SEM)	171.900 (32.378)	216.802 (83.414)
CV (%) Geometric Mean	357.9	730.9
Median	144.192	181.656
Min, Max	6.00, 5949.67	4.99, 15523.75
Change from baseline		
n	74	27
Mean (SD)	-46.294 (532.559)	350.239 (1444.097)
SE	61.909	277.917
Median	-7.484	11.924
Min, Max	-2250.32, 2879.02	-521.88, 7155.13

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Table 12.3
Cardiac Biomarkers - NT-proBNP (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Baseline NIS: <50

Subgroup Visit	Vutrisiran (HELIOS-A) (N=78)	Patisiran (HELIOS-A) (N=27)
Week 60		
Actual Value		
n	76	23
Mean (SD)	497.921 (916.173)	940.694 (2577.723)
SE	105.092	537.492
Geometric Mean (SEM)	153.956 (27.256)	184.601 (67.300)
CV (%) Geometric Mean	313.5	450.1
Median	125.713	107.742
Min, Max	9.98, 5021.60	10.99, 12454.12
Change from baseline		
n	76	23
Mean (SD)	-121.631 (479.990)	-61.872 (436.558)
SE	55.059	91.029
Median	-11.502	-1.015
Min, Max	-2485.85, 1385.17	-1870.10, 450.08

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Table 12.3
Cardiac Biomarkers - NT-proBNP (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Baseline NIS: <50

Subgroup Visit	Vutrisiran (HELIOS-A) (N=78)	Patisiran (HELIOS-A) (N=27)
Week 72		
Actual Value		
n	76	25
Mean (SD)	559.587 (1076.895)	1186.686 (3163.597)
SE	123.528	632.719
Geometric Mean (SEM)	153.372 (28.620)	169.478 (66.015)
CV (%) Geometric Mean	362.0	658.8
Median	134.720	102.753
Min, Max	4.99, 6525.42	4.99, 13774.34
Change from baseline		
n	76	25
Mean (SD)	18.058 (699.742)	186.727 (1169.359)
SE	80.266	233.872
Median	-9.514	0.000
Min, Max	-1111.67, 5402.75	-549.87, 5731.14

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Table 12.3
Cardiac Biomarkers - NT-proBNP (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Baseline NIS: <50

Subgroup Visit	Vutrisiran (HELIOS-A) (N=78)	Patisiran (HELIOS-A) (N=27)
Month 18		
Actual Value		
n	74	26
Mean (SD)	508.535 (885.127)	1260.766 (3230.565)
SE	102.894	633.566
Geometric Mean (SEM)	142.146 (26.872)	190.163 (72.378)
CV (%) Geometric Mean	361.6	649.8
Median	108.799	130.196
Min, Max	4.99, 3880.92	4.99, 15039.76
Change from baseline		
n	74	26
Mean (SD)	-32.931 (468.733)	233.865 (959.903)
SE	54.489	188.253
Median	-14.969	-6.004
Min, Max	-1725.40, 2123.55	-291.43, 4741.16

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Table 12.3
Cardiac Biomarkers - NT-proBNP (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Baseline NIS: ≥50

Subgroup Visit	Vutrisiran (HELIOS-A) (N=44)	Patisiran (HELIOS-A) (N=15)
Baseline		
n	44	15
Mean (SD)	1279.321 (1674.617)	1259.777 (1239.723)
SE	252.458	320.095
Geometric Mean (SEM)	546.811 (126.078)	697.785 (231.697)
CV (%) Geometric Mean	306.1	205.6
Median	705.060	770.433
Min, Max	14.97, 7588.21	62.84, 4200.25
Week 12		
Actual Value		
n	41	13
Mean (SD)	1229.786 (1631.447)	792.818 (626.265)
SE	254.789	173.695
Geometric Mean (SEM)	533.237 (121.966)	536.855 (156.415)
CV (%) Geometric Mean	274.6	141.9
Median	624.719	514.947
Min, Max	20.97, 7156.14	66.89, 2010.82
Change from baseline		
n	41	13
Mean (SD)	95.044 (770.930)	-184.304 (445.634)
SE	120.399	123.597
Median	-3.975	1.015
Min, Max	-1699.43, 2803.16	-1200.47, 218.61

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Table 12.3
Cardiac Biomarkers - NT-proBNP (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Baseline NIS: ≥50

Subgroup Visit	Vutrisiran (HELIOS-A) (N=44)	Patisiran (HELIOS-A) (N=15)
Week 24		
Actual Value		
n	42	11
Mean (SD)	1229.420 (1781.751)	1087.009 (1582.936)
SE	274.930	477.273
Geometric Mean (SEM)	502.509 (117.626)	510.937 (199.586)
CV (%) Geometric Mean	299.8	208.7
Median	583.787	349.274
Min, Max	19.96, 9061.17	57.85, 5480.64
Change from baseline		
n	42	11
Mean (SD)	107.678 (838.173)	-41.731 (611.603)
SE	129.333	184.405
Median	0.465	-8.034
Min, Max	-1500.86, 4519.59	-1187.53, 1280.39

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Table 12.3
Cardiac Biomarkers - NT-proBNP (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Baseline NIS: ≥50

Subgroup Visit	Vutrisiran (HELIOS-A) (N=44)	Patisiran (HELIOS-A) (N=15)
Month 9		
Actual Value		
n	39	13
Mean (SD)	1165.806 (1433.361)	1443.233 (2689.874)
SE	229.521	746.037
Geometric Mean (SEM)	576.050 (124.083)	596.803 (218.584)
CV (%) Geometric Mean	226.0	217.2
Median	622.689	542.855
Min, Max	18.94, 7455.52	70.87, 10173.86
Change from baseline		
n	39	13
Mean (SD)	-1.514 (912.416)	244.570 (1783.027)
SE	146.103	494.523
Median	38.902	4.990
Min, Max	-4190.27, 1647.59	-1179.50, 5973.60

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Table 12.3
Cardiac Biomarkers - NT-proBNP (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Baseline NIS: ≥50

Subgroup Visit	Vutrisiran (HELIOS-A) (N=44)	Patisiran (HELIOS-A) (N=15)
Week 48		
Actual Value		
n	40	12
Mean (SD)	1206.937 (1543.724)	1101.299 (1386.203)
SE	244.084	400.162
Geometric Mean (SEM)	484.889 (126.121)	557.296 (204.040)
CV (%) Geometric Mean	373.8	199.9
Median	588.776	455.579
Min, Max	7.95, 7502.37	81.86, 4828.95
Change from baseline		
n	40	12
Mean (SD)	55.078 (1222.643)	-133.050 (474.463)
SE	193.317	136.966
Median	-1.015	-6.977
Min, Max	-4292.10, 5112.34	-1159.62, 628.69

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Table 12.3
Cardiac Biomarkers - NT-proBNP (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Baseline NIS: ≥50

Subgroup Visit	Vutrisiran (HELIOS-A) (N=44)	Patisiran (HELIOS-A) (N=15)
Week 60		
Actual Value		
n	42	12
Mean (SD)	1088.899 (1260.249)	1065.540 (1794.805)
SE	194.461	518.116
Geometric Mean (SEM)	506.059 (113.855)	495.477 (176.099)
CV (%) Geometric Mean	271.7	188.5
Median	618.714	429.108
Min, Max	17.00, 4942.69	55.90, 6561.36
Change from baseline		
n	42	12
Mean (SD)	-32.843 (853.444)	-77.332 (951.854)
SE	131.689	274.777
Median	21.396	-43.892
Min, Max	-4326.01, 1489.87	-1470.93, 2361.11

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Table 12.3
Cardiac Biomarkers - NT-proBNP (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Baseline NIS: ≥50

Subgroup Visit	Vutrisiran (HELIOS-A) (N=44)	Patisiran (HELIOS-A) (N=15)
Week 72		
Actual Value		
n	42	12
Mean (SD)	1327.006 (2051.724)	876.173 (1170.308)
SE	316.588	337.839
Geometric Mean (SEM)	498.942 (120.929)	465.847 (160.247)
CV (%) Geometric Mean	328.5	177.1
Median	591.779	338.787
Min, Max	6.00, 8107.13	63.85, 4286.09
Change from baseline		
n	42	12
Mean (SD)	205.263 (1476.556)	-266.699 (637.448)
SE	227.838	184.015
Median	13.996	-75.859
Min, Max	-4150.36, 5487.58	-1682.44, 521.88

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Table 12.3
Cardiac Biomarkers - NT-proBNP (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Baseline NIS: ≥50

Subgroup Visit	Vutrisiran (HELIOS-A) (N=44)	Patisiran (HELIOS-A) (N=15)
Month 18		
Actual Value		
n	40	12
Mean (SD)	1452.511 (2103.053)	949.862 (1358.932)
SE	332.522	392.290
Geometric Mean (SEM)	540.695 (137.979)	509.026 (170.626)
CV (%) Geometric Mean	354.0	168.8
Median	533.890	490.506
Min, Max	12.94, 9582.12	60.89, 5066.50
Change from baseline		
n	40	12
Mean (SD)	322.933 (1616.022)	-193.010 (850.271)
SE	255.516	245.452
Median	32.940	-41.397
Min, Max	-4300.05, 7674.05	-1911.03, 866.25

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Table 12.3
Cardiac Biomarkers - NT-proBNP (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Previous Tetramer Stabilizer Use: Yes

Subgroup Visit	Vutrisiran (HELIOS-A) (N=75)	Patisiran (HELIOS-A) (N=33)
Baseline		
n	75	33
Mean (SD)	794.338 (1377.425)	827.064 (1087.828)
SE	159.051	189.367
Geometric Mean (SEM)	248.134 (45.154)	282.612 (85.836)
CV (%) Geometric Mean	331.4	447.1
Median	213.539	330.330
Min, Max	14.97, 7052.38	4.99, 4200.25
Week 12		
Actual Value		
n	72	30
Mean (SD)	799.659 (1445.342)	608.202 (724.719)
SE	170.335	132.315
Geometric Mean (SEM)	243.380 (46.653)	215.756 (67.116)
CV (%) Geometric Mean	361.8	415.1
Median	206.562	288.384
Min, Max	4.99, 7156.14	4.99, 2250.32
Change from baseline		
n	72	30
Mean (SD)	2.827 (468.159)	-93.735 (447.063)
SE	55.173	81.622
Median	-8.542	-26.428
Min, Max	-1699.43, 2614.57	-1200.47, 1348.13

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Table 12.3
Cardiac Biomarkers - NT-proBNP (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Previous Tetramer Stabilizer Use: Yes

Subgroup Visit	Vutrisiran (HELIOS-A) (N=75)	Patisiran (HELIOS-A) (N=33)
Week 24		
Actual Value		
n	73	30
Mean (SD)	834.607 (1683.273)	791.550 (1285.443)
SE	197.012	234.689
Geometric Mean (SEM)	234.676 (45.031)	232.204 (75.618)
CV (%) Geometric Mean	370.1	480.5
Median	239.502	295.361
Min, Max	4.99, 9061.17	4.99, 5480.64
Change from baseline		
n	73	30
Mean (SD)	40.503 (663.624)	31.336 (435.467)
SE	77.671	79.505
Median	-3.975	0.507
Min, Max	-1500.86, 4519.59	-1187.53, 1280.39

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Table 12.3
Cardiac Biomarkers - NT-proBNP (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Previous Tetramer Stabilizer Use: Yes

Subgroup Visit	Vutrisiran (HELIOS-A) (N=75)	Patisiran (HELIOS-A) (N=33)
Month 9		
Actual Value		
n	74	32
Mean (SD)	702.115 (1220.705)	993.938 (1974.387)
SE	141.904	349.026
Geometric Mean (SEM)	242.670 (42.137)	289.899 (87.790)
CV (%) Geometric Mean	288.3	422.1
Median	223.519	321.324
Min, Max	10.99, 7455.52	4.99, 10173.86
Change from baseline		
n	74	32
Mean (SD)	-81.488 (646.791)	182.285 (1186.572)
SE	75.188	209.758
Median	3.975	3.975
Min, Max	-4190.27, 1319.21	-1179.50, 5973.60

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

Alnylam Pharmaceuticals Inc.
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Table 12.3
Cardiac Biomarkers - NT-proBNP (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Previous Tetramer Stabilizer Use: Yes

Subgroup Visit	Vutrisiran (HELIOS-A) (N=75)	Patisiran (HELIOS-A) (N=33)
Week 48		
Actual Value		
n	70	31
Mean (SD)	715.710 (1199.774)	806.871 (1303.447)
SE	143.400	234.106
Geometric Mean (SEM)	221.719 (42.545)	250.955 (77.472)
CV (%) Geometric Mean	348.8	426.5
Median	200.093	272.400
Min, Max	6.00, 5949.67	4.99, 5318.95
Change from baseline		
n	70	31
Mean (SD)	-91.727 (682.832)	-6.111 (500.871)
SE	81.614	89.959
Median	-6.470	-6.004
Min, Max	-4292.10, 1747.30	-1159.62, 2112.64

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

Alnylam Pharmaceuticals Inc.
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Table 12.3
Cardiac Biomarkers - NT-proBNP (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Previous Tetramer Stabilizer Use: Yes

Subgroup Visit	Vutrisiran (HELIOS-A) (N=75)	Patisiran (HELIOS-A) (N=33)
Week 60		
Actual Value		
n	74	29
Mean (SD)	704.826 (1181.768)	702.368 (1267.767)
SE	137.378	235.418
Geometric Mean (SEM)	234.226 (41.821)	258.591 (70.433)
CV (%) Geometric Mean	309.5	275.6
Median	223.519	316.376
Min, Max	10.99, 5021.60	15.98, 6561.36
Change from baseline		
n	74	29
Mean (SD)	-78.777 (676.961)	-18.095 (620.914)
SE	78.695	115.301
Median	-1.015	-8.034
Min, Max	-4326.01, 1489.87	-1470.93, 2361.11

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Table 12.3
Cardiac Biomarkers - NT-proBNP (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Previous Tetramer Stabilizer Use: Yes

Subgroup Visit	Vutrisiran (HELIOS-A) (N=75)	Patisiran (HELIOS-A) (N=33)
Week 72		
Actual Value		
n	73	30
Mean (SD)	733.573 (1497.252)	820.321 (1750.266)
SE	175.240	319.553
Geometric Mean (SEM)	213.552 (39.800)	233.134 (69.883)
CV (%) Geometric Mean	340.9	371.7
Median	192.566	303.353
Min, Max	4.99, 8107.13	4.99, 8937.44
Change from baseline		
n	73	30
Mean (SD)	35.844 (958.126)	73.511 (1151.819)
SE	112.140	210.292
Median	-6.004	-0.507
Min, Max	-4150.36, 5487.58	-1682.44, 5731.14

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Table 12.3
Cardiac Biomarkers - NT-proBNP (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Previous Tetramer Stabilizer Use: Yes

Subgroup Visit	Vutrisiran (HELIOS-A) (N=75)	Patisiran (HELIOS-A) (N=33)
Month 18		
Actual Value		
n	70	31
Mean (SD)	796.588 (1651.277)	891.761 (1651.524)
SE	197.365	296.622
Geometric Mean (SEM)	203.958 (41.059)	254.594 (79.327)
CV (%) Geometric Mean	400.8	439.1
Median	196.583	329.316
Min, Max	4.99, 9582.12	4.99, 7947.47
Change from baseline		
n	70	31
Mean (SD)	103.386 (1189.929)	114.189 (1029.913)
SE	142.224	184.978
Median	-3.002	-4.990
Min, Max	-4300.05, 7674.05	-1911.03, 4741.16

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Table 12.3
Cardiac Biomarkers - NT-proBNP (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Previous Tetramer Stabilizer Use: No

Subgroup Visit	Vutrisiran (HELIOS-A) (N=47)	Patisiran (HELIOS-A) (N=9)
Baseline		
n	47	9
Mean (SD)	1354.860 (2982.265)	2553.027 (4657.363)
SE	435.008	1552.454
Geometric Mean (SEM)	317.959 (88.585)	484.570 (374.532)
CV (%) Geometric Mean	611.6	1467.2
Median	476.045	429.108
Min, Max	4.99, 18755.00	7.02, 14324.21
Week 12		
Actual Value		
n	46	8
Mean (SD)	1502.511 (4531.842)	2882.875 (5530.594)
SE	668.184	1955.360
Geometric Mean (SEM)	310.360 (85.133)	314.337 (302.795)
CV (%) Geometric Mean	555.5	4090.8
Median	493.466	317.307
Min, Max	7.02, 30496.62	4.99, 15851.04
Change from baseline		
n	46	8
Mean (SD)	283.159 (1805.731)	259.947 (566.026)
SE	266.241	200.121
Median	-4.482	-15.984
Min, Max	-1260.35, 11741.61	-130.75, 1526.83

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Table 12.3
Cardiac Biomarkers - NT-proBNP (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Previous Tetramer Stabilizer Use: No

Subgroup Visit	Vutrisiran (HELIOS-A) (N=47)	Patisiran (HELIOS-A) (N=9)
Week 24		
Actual Value		
n	45	8
Mean (SD)	1278.894 (3644.170)	2818.126 (5016.351)
SE	543.241	1773.548
Geometric Mean (SEM)	286.040 (77.566)	358.547 (315.600)
CV (%) Geometric Mean	513.4	2215.7
Median	375.237	267.410
Min, Max	14.97, 24392.27	7.95, 13526.89
Change from baseline		
n	45	8
Mean (SD)	68.990 (928.376)	195.198 (1085.507)
SE	138.394	383.785
Median	-2.030	-56.408
Min, Max	-1970.90, 5637.27	-797.33, 2801.21

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Table 12.3
Cardiac Biomarkers - NT-proBNP (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Previous Tetramer Stabilizer Use: No

Subgroup Visit	Vutrisiran (HELIOS-A) (N=47)	Patisiran (HELIOS-A) (N=9)
Month 9		
Actual Value		
n	39	6
Mean (SD)	843.605 (1081.243)	2479.691 (5357.843)
SE	173.138	2187.330
Geometric Mean (SEM)	276.985 (77.259)	312.493 (282.299)
CV (%) Geometric Mean	444.8	1152.5
Median	351.304	266.480
Min, Max	13.95, 3922.86	36.96, 13397.16
Change from baseline		
n	39	6
Mean (SD)	36.263 (585.039)	1441.341 (3568.052)
SE	93.681	1456.651
Median	2.030	15.941
Min, Max	-1712.46, 1722.44	-147.66, 8722.89

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Table 12.3
Cardiac Biomarkers - NT-proBNP (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Previous Tetramer Stabilizer Use: No

Subgroup Visit	Vutrisiran (HELIOS-A) (N=47)	Patisiran (HELIOS-A) (N=9)
Week 48		
Actual Value		
n	44	8
Mean (SD)	966.035 (1405.945)	3629.089 (6282.989)
SE	211.954	2221.372
Geometric Mean (SEM)	294.348 (81.513)	506.885 (413.370)
CV (%) Geometric Mean	531.1	1426.4
Median	395.703	350.796
Min, Max	7.95, 7502.37	18.94, 15523.75
Change from baseline		
n	44	8
Mean (SD)	118.142 (1033.267)	1006.161 (2524.036)
SE	155.771	892.382
Median	0.000	19.451
Min, Max	-2250.32, 5112.34	-203.64, 7155.13

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Table 12.3
Cardiac Biomarkers - NT-proBNP (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Previous Tetramer Stabilizer Use: No

Subgroup Visit	Vutrisiran (HELIOS-A) (N=47)	Patisiran (HELIOS-A) (N=9)
Week 60		
Actual Value		
n	44	6
Mean (SD)	714.061 (909.455)	2342.293 (4967.242)
SE	137.106	2027.868
Geometric Mean (SEM)	236.709 (62.500)	260.803 (266.711)
CV (%) Geometric Mean	452.6	2302.4
Median	336.800	270.920
Min, Max	9.98, 3817.07	10.99, 12454.12
Change from baseline		
n	44	6
Mean (SD)	-108.951 (568.069)	-304.382 (769.231)
SE	85.640	314.037
Median	-14.969	-7.992
Min, Max	-2485.85, 1427.03	-1870.10, 115.69

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Table 12.3
Cardiac Biomarkers - NT-proBNP (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Previous Tetramer Stabilizer Use: No

Subgroup Visit	Vutrisiran (HELIOS-A) (N=47)	Patisiran (HELIOS-A) (N=9)
Week 72		
Actual Value		
n	45	7
Mean (SD)	993.602 (1596.958)	2224.517 (5099.302)
SE	238.060	1927.355
Geometric Mean (SEM)	269.582 (74.987)	244.550 (228.786)
CV (%) Geometric Mean	561.4	2137.5
Median	334.305	355.279
Min, Max	6.00, 7362.66	7.95, 13774.34
Change from baseline		
n	45	7
Mean (SD)	163.930 (1172.670)	-105.362 (223.182)
SE	174.811	84.355
Median	4.990	-28.923
Min, Max	-1151.59, 5402.75	-549.87, 150.70

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Table 12.3
Cardiac Biomarkers - NT-proBNP (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Previous Tetramer Stabilizer Use: No

Subgroup Visit	Vutrisiran (HELIOS-A) (N=47)	Patisiran (HELIOS-A) (N=9)
Month 18		
Actual Value		
n	44	7
Mean (SD)	908.430 (1223.205)	2361.956 (5595.415)
SE	184.405	2114.868
Geometric Mean (SEM)	269.612 (74.159)	282.474 (224.822)
CV (%) Geometric Mean	518.7	912.6
Median	356.759	187.576
Min, Max	10.99, 5501.53	17.00, 15039.76
Change from baseline		
n	44	7
Mean (SD)	73.714 (738.533)	32.076 (322.481)
SE	111.338	121.886
Median	-13.489	-22.918
Min, Max	-1725.40, 3111.50	-291.43, 715.55

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Table 12.3
Cardiac Biomarkers - NT-proBNP (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Genotype: V30M

Subgroup Visit	Vutrisiran (HELIOS-A) (N=54)	Patisiran (HELIOS-A) (N=20)
Baseline		
n	54	20
Mean (SD)	445.837 (817.490)	576.552 (858.526)
SE	111.246	191.972
Geometric Mean (SEM)	153.452 (30.439)	203.216 (74.331)
CV (%) Geometric Mean	271.5	367.8
Median	111.802	210.072
Min, Max	9.98, 4516.63	4.99, 3206.30
Week 12		
Actual Value		
n	51	18
Mean (SD)	420.149 (844.620)	395.736 (591.748)
SE	118.270	139.476
Geometric Mean (SEM)	145.156 (29.581)	141.243 (54.316)
CV (%) Geometric Mean	270.5	365.0
Median	137.680	94.803
Min, Max	7.02, 5408.76	4.99, 2250.32
Change from baseline		
n	51	18
Mean (SD)	-8.709 (261.361)	-131.835 (319.646)
SE	36.598	75.341
Median	0.000	-34.420
Min, Max	-1201.49, 892.13	-955.98, 201.53

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Table 12.3
Cardiac Biomarkers - NT-proBNP (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Genotype: V30M

Subgroup Visit	Vutrisiran (HELIOS-A) (N=54)	Patisiran (HELIOS-A) (N=20)
Week 24		
Actual Value		
n	53	18
Mean (SD)	411.369 (893.638)	493.635 (1053.903)
SE	122.751	248.407
Geometric Mean (SEM)	133.477 (26.803)	129.993 (53.014)
CV (%) Geometric Mean	273.4	435.4
Median	95.818	122.246
Min, Max	4.99, 5784.00	4.99, 4438.74
Change from baseline		
n	53	18
Mean (SD)	-12.904 (262.836)	28.937 (353.249)
SE	36.103	83.262
Median	0.000	-3.002
Min, Max	-953.02, 1267.37	-647.64, 1232.44

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Table 12.3
Cardiac Biomarkers - NT-proBNP (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Genotype: V30M

Subgroup Visit	Vutrisiran (HELIOS-A) (N=54)	Patisiran (HELIOS-A) (N=20)
Month 9		
Actual Value		
n	50	19
Mean (SD)	449.119 (736.307)	617.615 (1245.332)
SE	104.130	285.699
Geometric Mean (SEM)	164.827 (33.075)	181.173 (70.336)
CV (%) Geometric Mean	254.7	406.5
Median	126.728	225.548
Min, Max	10.99, 3346.01	4.99, 5444.70
Change from baseline		
n	50	19
Mean (SD)	11.464 (371.382)	33.303 (604.446)
SE	52.521	138.669
Median	8.964	-8.964
Min, Max	-1226.43, 1722.44	-950.06, 2238.40

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Table 12.3
Cardiac Biomarkers - NT-proBNP (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Genotype: V30M

Subgroup Visit	Vutrisiran (HELIOS-A) (N=54)	Patisiran (HELIOS-A) (N=20)
Week 48		
Actual Value		
n	49	19
Mean (SD)	492.137 (911.961)	534.834 (1203.511)
SE	130.280	276.104
Geometric Mean (SEM)	142.387 (32.286)	152.245 (57.528)
CV (%) Geometric Mean	337.9	375.1
Median	129.730	145.714
Min, Max	7.95, 4001.68	4.99, 5318.95
Change from baseline		
n	49	19
Mean (SD)	63.148 (528.711)	-31.513 (597.895)
SE	75.530	137.166
Median	-6.004	-19.959
Min, Max	-1742.40, 2879.02	-1159.62, 2112.64

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Table 12.3
Cardiac Biomarkers - NT-proBNP (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Genotype: V30M

Subgroup Visit	Vutrisiran (HELIOS-A) (N=54)	Patisiran (HELIOS-A) (N=20)
Week 60		
Actual Value		
n	52	17
Mean (SD)	418.776 (836.142)	294.214 (323.670)
SE	115.952	78.501
Geometric Mean (SEM)	136.165 (27.520)	165.078 (47.285)
CV (%) Geometric Mean	271.4	174.2
Median	105.755	118.736
Min, Max	10.99, 4942.69	15.98, 1114.72
Change from baseline		
n	52	17
Mean (SD)	7.933 (220.211)	-169.941 (353.324)
SE	30.538	85.694
Median	0.973	-16.914
Min, Max	-928.07, 726.46	-1281.32, 121.70

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Table 12.3
Cardiac Biomarkers - NT-proBNP (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Genotype: V30M

Subgroup Visit	Vutrisiran (HELIOS-A) (N=54)	Patisiran (HELIOS-A) (N=20)
Week 72		
Actual Value		
n	53	20
Mean (SD)	597.757 (1449.257)	740.402 (1971.803)
SE	199.071	440.909
Geometric Mean (SEM)	145.652 (32.418)	166.603 (63.134)
CV (%) Geometric Mean	357.9	408.3
Median	134.720	181.107
Min, Max	6.00, 8107.13	4.99, 8937.44
Change from baseline		
n	53	20
Mean (SD)	173.483 (916.766)	163.850 (1349.350)
SE	125.927	301.724
Median	6.935	-25.456
Min, Max	-1111.67, 5402.75	-1215.52, 5731.14

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Table 12.3
Cardiac Biomarkers - NT-proBNP (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Genotype: V30M

Subgroup Visit	Vutrisiran (HELIOS-A) (N=54)	Patisiran (HELIOS-A) (N=20)
Month 18		
Actual Value		
n	51	20
Mean (SD)	453.803 (829.104)	693.009 (1748.687)
SE	116.098	391.018
Geometric Mean (SEM)	131.342 (29.268)	170.341 (64.170)
CV (%) Geometric Mean	340.4	401.1
Median	110.787	170.113
Min, Max	4.99, 3448.85	4.99, 7947.47
Change from baseline		
n	51	20
Mean (SD)	35.453 (384.574)	116.457 (1168.181)
SE	53.851	261.213
Median	0.000	-18.944
Min, Max	-1067.78, 1332.23	-1591.69, 4741.16

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Table 12.3
Cardiac Biomarkers - NT-proBNP (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Genotype: non-V30M

Subgroup Visit	Vutrisiran (HELIOS-A) (N=68)	Patisiran (HELIOS-A) (N=22)
Baseline		
n	68	22
Mean (SD)	1458.508 (2710.709)	1760.878 (3114.965)
SE	328.722	664.113
Geometric Mean (SEM)	431.380 (92.308)	475.551 (202.860)
CV (%) Geometric Mean	463.7	733.3
Median	577.275	535.413
Min, Max	4.99, 18755.00	7.02, 14324.21
Week 12		
Actual Value		
n	67	20
Mean (SD)	1571.095 (3916.454)	1709.291 (3552.045)
SE	478.471	794.261
Geometric Mean (SEM)	426.210 (91.935)	367.225 (171.772)
CV (%) Geometric Mean	464.6	886.1
Median	526.871	597.741
Min, Max	4.99, 30496.62	4.99, 15851.04
Change from baseline		
n	67	20
Mean (SD)	204.075 (1555.880)	82.029 (591.990)
SE	190.081	132.373
Median	-10.994	-7.992
Min, Max	-1699.43, 11741.61	-1200.47, 1526.83

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Table 12.3
Cardiac Biomarkers - NT-proBNP (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Genotype: non-V30M

Subgroup Visit	Vutrisiran (HELIOS-A) (N=68)	Patisiran (HELIOS-A) (N=22)
Week 24		
Actual Value		
n	65	20
Mean (SD)	1487.292 (3350.598)	1870.304 (3349.527)
SE	415.591	748.977
Geometric Mean (SEM)	426.381 (91.050)	465.689 (200.620)
CV (%) Geometric Mean	428.7	631.9
Median	572.793	575.795
Min, Max	4.99, 24392.27	7.95, 13526.89
Change from baseline		
n	65	20
Mean (SD)	103.773 (1012.919)	99.040 (786.373)
SE	125.637	175.838
Median	-6.935	-12.009
Min, Max	-1970.90, 5637.27	-1187.53, 2801.21

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Table 12.3
Cardiac Biomarkers - NT-proBNP (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Genotype: non-V30M

Subgroup Visit	Vutrisiran (HELIOS-A) (N=68)	Patisiran (HELIOS-A) (N=22)
Month 9		
Actual Value		
n	63	19
Mean (SD)	990.495 (1385.292)	1839.446 (3601.177)
SE	174.530	826.167
Geometric Mean (SEM)	358.012 (73.179)	474.998 (190.678)
CV (%) Geometric Mean	359.2	451.3
Median	355.279	542.855
Min, Max	13.95, 7455.52	30.95, 13397.16
Change from baseline		
n	63	19
Mean (SD)	-82.366 (771.419)	728.864 (2405.301)
SE	97.190	551.814
Median	-9.979	23.003
Min, Max	-4190.27, 1647.59	-1179.50, 8722.89

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

Alnylam Pharmaceuticals Inc.
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Table 12.3
Cardiac Biomarkers - NT-proBNP (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Genotype: non-V30M

Subgroup Visit	Vutrisiran (HELIOS-A) (N=68)	Patisiran (HELIOS-A) (N=22)
Week 48		
Actual Value		
n	65	20
Mean (SD)	1053.701 (1464.592)	2194.194 (4136.162)
SE	181.660	924.874
Geometric Mean (SEM)	375.053 (77.574)	534.470 (220.740)
CV (%) Geometric Mean	389.0	541.4
Median	403.145	523.404
Min, Max	6.00, 7502.37	18.94, 15523.75
Change from baseline		
n	65	20
Mean (SD)	-66.413 (1010.752)	422.930 (1625.304)
SE	125.368	363.429
Median	-3.975	14.969
Min, Max	-4292.10, 5112.34	-724.43, 7155.13

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

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Table 12.3
Cardiac Biomarkers - NT-proBNP (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Genotype: non-V30M

Subgroup Visit	Vutrisiran (HELIOS-A) (N=68)	Patisiran (HELIOS-A) (N=22)
Week 60		
Actual Value		
n	66	18
Mean (SD)	936.355 (1203.014)	1634.489 (3109.365)
SE	148.081	732.884
Geometric Mean (SEM)	361.650 (71.577)	396.225 (179.205)
CV (%) Geometric Mean	350.3	622.3
Median	412.659	526.913
Min, Max	9.98, 5021.60	10.99, 12454.12
Change from baseline		
n	66	18
Mean (SD)	-167.210 (822.662)	29.886 (833.648)
SE	101.263	196.493
Median	-8.499	1.480
Min, Max	-4326.01, 1489.87	-1870.10, 2361.11

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

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Table 12.3
Cardiac Biomarkers - NT-proBNP (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Genotype: non-V30M

Subgroup Visit	Vutrisiran (HELIOS-A) (N=68)	Patisiran (HELIOS-A) (N=22)
Week 72		
Actual Value		
n	65	17
Mean (SD)	1024.335 (1585.928)	1492.541 (3325.821)
SE	196.710	806.630
Geometric Mean (SEM)	342.818 (71.183)	353.044 (159.036)
CV (%) Geometric Mean	393.5	552.2
Median	391.221	405.175
Min, Max	4.99, 7395.65	7.95, 13774.34
Change from baseline		
n	65	17
Mean (SD)	12.290 (1136.039)	-106.424 (480.164)
SE	140.908	116.457
Median	-11.924	0.930
Min, Max	-4150.36, 5487.58	-1682.44, 521.88

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Table 12.3
Cardiac Biomarkers - NT-proBNP (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Genotype: non-V30M

Subgroup Visit	Vutrisiran (HELIOS-A) (N=68)	Patisiran (HELIOS-A) (N=22)
Month 18		
Actual Value		
n	63	18
Mean (SD)	1152.192 (1817.042)	1684.338 (3553.050)
SE	228.926	837.462
Geometric Mean (SEM)	353.929 (77.371)	414.305 (176.512)
CV (%) Geometric Mean	439.3	502.4
Median	424.119	390.713
Min, Max	10.99, 9582.12	17.00, 15039.76
Change from baseline		
n	63	18
Mean (SD)	137.656 (1352.938)	79.735 (620.389)
SE	170.454	146.227
Median	-14.969	10.487
Min, Max	-4300.05, 7674.05	-1911.03, 947.01

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Table 12.3
Cardiac Biomarkers - NT-proBNP (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

FAP Stage: I

Subgroup Visit	Vutrisiran (HELIOS-A) (N=84)	Patisiran (HELIOS-A) (N=31)
Baseline		
n	84	31
Mean (SD)	690.184 (2180.212)	669.636 (991.005)
SE	237.881	177.990
Geometric Mean (SEM)	155.372 (27.366)	213.994 (68.479)
CV (%) Geometric Mean	354.2	478.7
Median	100.765	254.471
Min, Max	4.99, 18755.00	4.99, 4200.25
Week 12		
Actual Value		
n	83	27
Mean (SD)	869.257 (3460.099)	451.391 (648.086)
SE	379.795	124.724
Geometric Mean (SEM)	158.556 (29.060)	135.807 (46.596)
CV (%) Geometric Mean	390.5	479.7
Median	125.756	104.782
Min, Max	4.99, 30496.62	4.99, 2250.32
Change from baseline		
n	83	27
Mean (SD)	171.071 (1328.453)	-12.679 (370.594)
SE	145.817	71.321
Median	-3.045	-29.938
Min, Max	-524.84, 11741.61	-955.98, 1348.13

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Table 12.3
Cardiac Biomarkers - NT-proBNP (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

FAP Stage: I

Subgroup Visit	Vutrisiran (HELIOS-A) (N=84)	Patisiran (HELIOS-A) (N=31)
Week 24		
Actual Value		
n	83	30
Mean (SD)	770.300 (2854.396)	684.402 (1264.993)
SE	313.311	230.955
Geometric Mean (SEM)	151.223 (27.146)	180.603 (59.630)
CV (%) Geometric Mean	367.5	503.2
Median	113.747	203.560
Min, Max	4.99, 24392.27	4.99, 5480.64
Change from baseline		
n	83	30
Mean (SD)	72.006 (840.401)	58.906 (365.157)
SE	92.246	66.668
Median	-2.960	-3.002
Min, Max	-1970.90, 5637.27	-647.64, 1280.39

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Table 12.3
Cardiac Biomarkers - NT-proBNP (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

FAP Stage: I

Subgroup Visit	Vutrisiran (HELIOS-A) (N=84)	Patisiran (HELIOS-A) (N=31)
Month 9		
Actual Value		
n	80	29
Mean (SD)	432.981 (777.435)	925.735 (2066.348)
SE	86.920	383.711
Geometric Mean (SEM)	147.012 (23.636)	226.480 (73.636)
CV (%) Geometric Mean	262.8	452.2
Median	118.736	225.548
Min, Max	10.99, 3922.86	4.99, 10173.86
Change from baseline		
n	80	29
Mean (SD)	-49.727 (579.160)	293.467 (1189.535)
SE	64.752	220.891
Median	3.002	2.960
Min, Max	-4190.27, 1722.44	-606.71, 5973.60

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Table 12.3
Cardiac Biomarkers - NT-proBNP (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

FAP Stage: I

Subgroup Visit	Vutrisiran (HELIOS-A) (N=84)	Patisiran (HELIOS-A) (N=31)
Week 48		
Actual Value		
n	80	30
Mean (SD)	424.903 (759.023)	672.069 (1275.286)
SE	84.861	232.834
Geometric Mean (SEM)	135.432 (23.271)	197.863 (60.628)
CV (%) Geometric Mean	310.0	396.5
Median	122.246	248.002
Min, Max	6.00, 4001.68	4.99, 5318.95
Change from baseline		
n	80	30
Mean (SD)	-59.664 (668.042)	46.573 (440.783)
SE	74.689	80.476
Median	-7.484	-3.002
Min, Max	-4292.10, 2879.02	-521.88, 2112.64

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Table 12.3
Cardiac Biomarkers - NT-proBNP (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

FAP Stage: I

Subgroup Visit	Vutrisiran (HELIOS-A) (N=84)	Patisiran (HELIOS-A) (N=31)
Week 60		
Actual Value		
n	82	27
Mean (SD)	380.411 (686.012)	652.902 (1302.626)
SE	75.757	250.690
Geometric Mean (SEM)	130.394 (21.045)	203.636 (62.208)
CV (%) Geometric Mean	273.2	338.0
Median	106.262	253.456
Min, Max	9.98, 4222.24	10.99, 6561.36
Change from baseline		
n	82	27
Mean (SD)	-84.196 (604.481)	92.736 (505.966)
SE	66.754	97.373
Median	-3.975	-1.015
Min, Max	-4326.01, 1385.17	-635.63, 2361.11

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Table 12.3
Cardiac Biomarkers - NT-proBNP (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

FAP Stage: I

Subgroup Visit	Vutrisiran (HELIOS-A) (N=84)	Patisiran (HELIOS-A) (N=31)
Week 72		
Actual Value		
n	83	29
Mean (SD)	460.995 (971.745)	766.677 (1778.012)
SE	106.663	330.168
Geometric Mean (SEM)	132.896 (22.829)	185.223 (60.489)
CV (%) Geometric Mean	325.3	458.7
Median	112.732	259.461
Min, Max	4.99, 6525.42	4.99, 8937.44
Change from baseline		
n	83	29
Mean (SD)	-11.540 (787.500)	178.247 (1088.225)
SE	86.439	202.078
Median	-6.004	0.930
Min, Max	-4150.36, 5402.75	-615.67, 5731.14

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Table 12.3
Cardiac Biomarkers - NT-proBNP (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

FAP Stage: I

Subgroup Visit	Vutrisiran (HELIOS-A) (N=84)	Patisiran (HELIOS-A) (N=31)
Month 18		
Actual Value		
n	80	30
Mean (SD)	411.019 (790.829)	839.690 (1687.467)
SE	88.417	308.088
Geometric Mean (SEM)	121.961 (21.032)	208.152 (67.198)
CV (%) Geometric Mean	313.0	466.9
Median	105.797	195.061
Min, Max	4.99, 3880.92	4.99, 7947.47
Change from baseline		
n	80	30
Mean (SD)	-57.257 (647.039)	214.193 (914.756)
SE	72.341	167.011
Median	-8.499	-6.004
Min, Max	-4300.05, 2123.55	-616.68, 4741.16

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Table 12.3
Cardiac Biomarkers - NT-proBNP (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

FAP Stage: II&III

Subgroup Visit	Vutrisiran (HELIOS-A) (N=38)	Patisiran (HELIOS-A) (N=11)
Baseline		
n	38	11
Mean (SD)	1717.850 (1920.303)	2682.876 (4124.212)
SE	311.514	1243.497
Geometric Mean (SEM)	949.086 (181.465)	962.025 (493.149)
CV (%) Geometric Mean	173.5	412.3
Median	945.535	1320.222
Min, Max	84.82, 7588.21	62.84, 14324.21
Week 12		
Actual Value		
n	35	11
Mean (SD)	1558.359 (1653.509)	2647.410 (4619.635)
SE	279.494	1392.872
Geometric Mean (SEM)	925.503 (169.662)	883.665 (437.718)
CV (%) Geometric Mean	149.7	372.4
Median	906.083	1456.972
Min, Max	153.66, 6818.79	66.89, 15851.04
Change from baseline		
n	35	11
Mean (SD)	-27.715 (743.827)	-35.466 (724.841)
SE	125.730	218.548
Median	-37.887	1.015
Min, Max	-1699.43, 2803.16	-1200.47, 1526.83

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Table 12.3
Cardiac Biomarkers - NT-proBNP (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

FAP Stage: II&III

Subgroup Visit	Vutrisiran (HELIOS-A) (N=38)	Patisiran (HELIOS-A) (N=11)
Week 24		
Actual Value		
n	35	8
Mean (SD)	1558.333 (1802.206)	3219.929 (4825.446)
SE	304.628	1706.053
Geometric Mean (SEM)	858.175 (170.011)	920.117 (617.935)
CV (%) Geometric Mean	171.7	599.2
Median	760.453	1101.228
Min, Max	77.80, 8382.58	57.85, 13526.89
Change from baseline		
n	35	8
Mean (SD)	2.424 (584.616)	91.811 (1197.824)
SE	98.818	423.495
Median	7.950	-73.364
Min, Max	-1500.86, 1491.90	-1187.53, 2801.21

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Table 12.3
Cardiac Biomarkers - NT-proBNP (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

FAP Stage: II&III

Subgroup Visit	Vutrisiran (HELIOS-A) (N=38)	Patisiran (HELIOS-A) (N=11)
Month 9		
Actual Value		
n	33	9
Mean (SD)	1521.776 (1563.964)	2204.204 (4253.670)
SE	272.251	1417.890
Geometric Mean (SEM)	956.235 (169.919)	675.231 (368.554)
CV (%) Geometric Mean	135.5	368.8
Median	1093.744	542.855
Min, Max	153.66, 7455.52	70.87, 13397.16
Change from baseline		
n	33	9
Mean (SD)	-19.323 (736.944)	663.405 (3056.780)
SE	128.286	1018.927
Median	38.902	4.990
Min, Max	-2109.68, 1416.04	-1179.50, 8722.89

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Table 12.3
Cardiac Biomarkers - NT-proBNP (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

FAP Stage: II&III

Subgroup Visit	Vutrisiran (HELIOS-A) (N=38)	Patisiran (HELIOS-A) (N=11)
Week 48		
Actual Value		
n	34	9
Mean (SD)	1723.912 (1742.849)	3764.850 (5750.696)
SE	298.896	1916.899
Geometric Mean (SEM)	1020.408 (195.555)	1035.357 (649.928)
CV (%) Geometric Mean	157.7	580.4
Median	1335.233	1236.413
Min, Max	112.73, 7502.37	81.86, 15523.75
Change from baseline		
n	34	9
Mean (SD)	104.427 (1146.428)	718.074 (2497.032)
SE	196.611	832.344
Median	39.410	15.984
Min, Max	-1742.40, 5112.34	-1159.62, 7155.13

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Table 12.3
Cardiac Biomarkers - NT-proBNP (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

FAP Stage: II&III

Subgroup Visit	Vutrisiran (HELIOS-A) (N=38)	Patisiran (HELIOS-A) (N=11)
Week 60		
Actual Value		
n	36	8
Mean (SD)	1455.057 (1419.328)	2099.260 (4220.898)
SE	236.555	1492.313
Geometric Mean (SEM)	900.845 (155.742)	582.869 (341.975)
CV (%) Geometric Mean	139.0	383.4
Median	806.840	450.039
Min, Max	138.69, 5021.60	55.90, 12454.12
Change from baseline		
n	36	8
Mean (SD)	-103.314 (712.124)	-606.864 (800.394)
SE	118.687	282.982
Median	-1.015	-200.093
Min, Max	-2030.78, 1489.87	-1870.10, 121.70

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Table 12.3
Cardiac Biomarkers - NT-proBNP (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

FAP Stage: II&III

Subgroup Visit	Vutrisiran (HELIOS-A) (N=38)	Patisiran (HELIOS-A) (N=11)
Week 72		
Actual Value		
n	35	8
Mean (SD)	1714.294 (2165.231)	2243.452 (4688.225)
SE	365.991	1657.538
Geometric Mean (SEM)	887.360 (177.628)	559.699 (340.098)
CV (%) Geometric Mean	175.1	426.4
Median	956.994	492.959
Min, Max	124.74, 8107.13	63.85, 13774.34
Change from baseline		
n	35	8
Mean (SD)	312.895 (1471.451)	-462.672 (678.243)
SE	248.721	239.795
Median	14.969	-298.405
Min, Max	-1151.59, 5487.58	-1682.44, 323.31

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Table 12.3
Cardiac Biomarkers - NT-proBNP (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

FAP Stage: II&III

Subgroup Visit	Vutrisiran (HELIOS-A) (N=38)	Patisiran (HELIOS-A) (N=11)
Month 18		
Actual Value		
n	34	8
Mean (SD)	1848.546 (2160.991)	2373.446 (5135.103)
SE	370.607	1815.533
Geometric Mean (SEM)	981.397 (205.697)	593.389 (348.831)
CV (%) Geometric Mean	185.8	385.7
Median	1019.914	607.255
Min, Max	72.81, 9582.12	60.89, 15039.76
Change from baseline		
n	34	8
Mean (SD)	442.970 (1577.610)	-332.677 (950.840)
SE	270.558	336.173
Median	121.273	-41.397
Min, Max	-1256.46, 7674.05	-1911.03, 715.55

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Table 12.3
Cardiac Biomarkers - NT-proBNP (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Cardiac Subpopulation: Yes

Subgroup Visit	Vutrisiran (HELIOS-A) (N=40)	Patisiran (HELIOS-A) (N=14)
Baseline		
n	40	14
Mean (SD)	1809.284 (3212.699)	2283.179 (3682.737)
SE	507.972	984.253
Geometric Mean (SEM)	748.070 (163.184)	872.034 (368.747)
CV (%) Geometric Mean	238.9	335.0
Median	824.769	1220.937
Min, Max	54.89, 18755.00	65.88, 14324.21
Week 12		
Actual Value		
n	38	12
Mean (SD)	2097.040 (4972.329)	2144.956 (4371.660)
SE	806.618	1261.989
Geometric Mean (SEM)	716.157 (184.463)	676.147 (317.892)
CV (%) Geometric Mean	338.3	363.2
Median	822.824	935.556
Min, Max	4.99, 30496.62	63.85, 15851.04
Change from baseline		
n	38	12
Mean (SD)	407.714 (2045.557)	-44.075 (803.207)
SE	331.833	231.866
Median	-10.487	-64.865
Min, Max	-1699.43, 11741.61	-1200.47, 1526.83

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Table 12.3
Cardiac Biomarkers - NT-proBNP (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Cardiac Subpopulation: Yes

Subgroup Visit	Vutrisiran (HELIOS-A) (N=40)	Patisiran (HELIOS-A) (N=14)
Week 24		
Actual Value		
n	39	13
Mean (SD)	1887.078 (4058.922)	2189.368 (3696.536)
SE	649.948	1025.235
Geometric Mean (SEM)	664.056 (167.288)	779.377 (342.359)
CV (%) Geometric Mean	329.9	336.0
Median	629.708	918.092
Min, Max	4.99, 24392.27	57.85, 13526.89
Change from baseline		
n	39	13
Mean (SD)	225.971 (1231.247)	-85.129 (605.897)
SE	197.157	168.046
Median	22.918	-8.034
Min, Max	-1500.86, 5637.27	-1187.53, 1280.39

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Table 12.3
Cardiac Biomarkers - NT-proBNP (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Cardiac Subpopulation: Yes

Subgroup Visit	Vutrisiran (HELIOS-A) (N=40)	Patisiran (HELIOS-A) (N=14)
Month 9		
Actual Value		
n	37	13
Mean (SD)	1246.756 (1443.597)	1621.857 (2644.014)
SE	237.326	733.318
Geometric Mean (SEM)	680.019 (135.414)	731.543 (277.894)
CV (%) Geometric Mean	182.7	235.1
Median	630.723	1159.624
Min, Max	43.89, 7455.52	70.87, 10173.86
Change from baseline		
n	37	13
Mean (SD)	10.411 (929.624)	264.912 (1789.980)
SE	152.829	496.451
Median	10.994	4.990
Min, Max	-4190.27, 1647.59	-1179.50, 5973.60

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Table 12.3
Cardiac Biomarkers - NT-proBNP (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Cardiac Subpopulation: Yes

Subgroup Visit	Vutrisiran (HELIOS-A) (N=40)	Patisiran (HELIOS-A) (N=14)
Week 48		
Actual Value		
n	37	14
Mean (SD)	1308.682 (1559.277)	2226.166 (4028.146)
SE	256.344	1076.567
Geometric Mean (SEM)	640.227 (149.474)	837.404 (327.994)
CV (%) Geometric Mean	255.2	275.1
Median	687.554	948.030
Min, Max	6.00, 7502.37	81.86, 15523.75
Change from baseline		
n	37	14
Mean (SD)	80.591 (1236.592)	-57.012 (578.067)
SE	203.294	154.495
Median	25.878	4.017
Min, Max	-4292.10, 5112.34	-1159.62, 1199.54

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Table 12.3
Cardiac Biomarkers - NT-proBNP (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Cardiac Subpopulation: Yes

Subgroup Visit	Vutrisiran (HELIOS-A) (N=40)	Patisiran (HELIOS-A) (N=14)
Week 60		
Actual Value		
n	38	13
Mean (SD)	1131.491 (1246.845)	2135.262 (3543.653)
SE	202.265	982.833
Geometric Mean (SEM)	575.792 (125.397)	730.366 (326.421)
CV (%) Geometric Mean	225.0	352.4
Median	623.196	910.142
Min, Max	12.94, 4783.03	55.90, 12454.12
Change from baseline		
n	38	13
Mean (SD)	-79.776 (906.222)	-179.841 (1061.926)
SE	147.009	294.525
Median	-1.987	-12.939
Min, Max	-4326.01, 1489.87	-1870.10, 2361.11

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Table 12.3
Cardiac Biomarkers - NT-proBNP (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Cardiac Subpopulation: Yes

Subgroup Visit	Vutrisiran (HELIOS-A) (N=40)	Patisiran (HELIOS-A) (N=14)
Week 72		
Actual Value		
n	38	13
Mean (SD)	1327.088 (1828.984)	2016.955 (3704.786)
SE	296.700	1027.523
Geometric Mean (SEM)	610.061 (140.559)	716.363 (301.639)
CV (%) Geometric Mean	255.3	300.4
Median	589.791	1101.693
Min, Max	4.99, 7395.65	63.85, 13774.34
Change from baseline		
n	38	13
Mean (SD)	115.821 (1456.433)	-298.148 (606.902)
SE	236.265	168.324
Median	15.984	-2.030
Min, Max	-4150.36, 5487.58	-1682.44, 521.88

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Table 12.3
Cardiac Biomarkers - NT-proBNP (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Cardiac Subpopulation: Yes

Subgroup Visit	Vutrisiran (HELIOS-A) (N=40)	Patisiran (HELIOS-A) (N=14)
Month 18		
Actual Value		
n	36	13
Mean (SD)	1506.203 (2154.186)	2231.828 (4061.031)
SE	359.031	1126.327
Geometric Mean (SEM)	614.367 (154.664)	808.716 (336.277)
CV (%) Geometric Mean	296.5	291.0
Median	611.230	1231.424
Min, Max	12.01, 9582.12	60.89, 15039.76
Change from baseline		
n	36	13
Mean (SD)	275.961 (1692.215)	-83.275 (871.843)
SE	282.036	241.806
Median	0.973	-4.990
Min, Max	-4300.05, 7674.05	-1911.03, 947.01

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Table 12.3
Cardiac Biomarkers - NT-proBNP (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Cardiac Subpopulation: No

Subgroup Visit	Vutrisiran (HELIOS-A) (N=82)	Patisiran (HELIOS-A) (N=28)
Baseline		
n	82	28
Mean (SD)	620.517 (1207.324)	653.780 (1077.875)
SE	133.327	203.699
Geometric Mean (SEM)	166.965 (30.296)	191.332 (65.450)
CV (%) Geometric Mean	372.5	504.8
Median	135.227	245.507
Min, Max	4.99, 7052.38	4.99, 4674.27
Week 12		
Actual Value		
n	80	26
Mean (SD)	587.543 (1195.373)	598.830 (1134.365)
SE	133.647	222.467
Geometric Mean (SEM)	167.629 (29.643)	142.985 (52.625)
CV (%) Geometric Mean	334.7	573.1
Median	137.215	114.254
Min, Max	7.02, 6818.79	4.99, 5270.06
Change from baseline		
n	80	26
Mean (SD)	-28.303 (245.980)	-7.829 (262.411)
SE	27.501	51.463
Median	-4.482	-12.939
Min, Max	-1201.49, 892.13	-955.98, 595.80

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Table 12.3
Cardiac Biomarkers - NT-proBNP (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Cardiac Subpopulation: No

Subgroup Visit	Vutrisiran (HELIOS-A) (N=82)	Patisiran (HELIOS-A) (N=28)
Week 24		
Actual Value		
n	79	25
Mean (SD)	568.108 (1252.444)	713.189 (1675.739)
SE	140.911	335.148
Geometric Mean (SEM)	157.189 (27.743)	142.164 (52.550)
CV (%) Geometric Mean	327.3	542.6
Median	123.726	123.726
Min, Max	4.99, 8382.58	4.99, 7475.48
Change from baseline		
n	79	25
Mean (SD)	-34.830 (362.880)	144.334 (614.461)
SE	40.827	122.892
Median	-2.960	-6.004
Min, Max	-1970.90, 1330.20	-226.56, 2801.21

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Table 12.3
Cardiac Biomarkers - NT-proBNP (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Cardiac Subpopulation: No

Subgroup Visit	Vutrisiran (HELIOS-A) (N=82)	Patisiran (HELIOS-A) (N=28)
Month 9		
Actual Value		
n	76	25
Mean (SD)	509.568 (932.157)	1024.001 (2803.149)
SE	106.926	560.630
Geometric Mean (SEM)	157.263 (27.354)	182.403 (65.119)
CV (%) Geometric Mean	299.5	481.7
Median	125.248	162.628
Min, Max	10.99, 4942.69	4.99, 13397.16
Change from baseline		
n	76	25
Mean (SD)	-65.803 (410.582)	441.493 (1786.478)
SE	47.097	357.296
Median	3.002	2.960
Min, Max	-2109.68, 1722.44	-392.24, 8722.89

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Table 12.3
Cardiac Biomarkers - NT-proBNP (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Cardiac Subpopulation: No

Subgroup Visit	Vutrisiran (HELIOS-A) (N=82)	Patisiran (HELIOS-A) (N=28)
Week 48		
Actual Value		
n	77	25
Mean (SD)	573.818 (1057.483)	915.176 (2513.197)
SE	120.511	502.639
Geometric Mean (SEM)	156.613 (29.166)	160.039 (57.152)
CV (%) Geometric Mean	366.7	482.1
Median	129.730	181.656
Min, Max	7.95, 5949.67	4.99, 11829.40
Change from baseline		
n	77	25
Mean (SD)	-54.604 (559.180)	346.321 (1483.709)
SE	63.725	296.742
Median	-7.019	0.000
Min, Max	-2250.32, 2879.02	-226.56, 7155.13

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Table 12.3
Cardiac Biomarkers - NT-proBNP (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Cardiac Subpopulation: No

Subgroup Visit	Vutrisiran (HELIOS-A) (N=82)	Patisiran (HELIOS-A) (N=28)
Week 60		
Actual Value		
n	80	22
Mean (SD)	507.239 (941.030)	302.911 (414.871)
SE	105.210	88.451
Geometric Mean (SEM)	153.676 (26.819)	140.335 (40.364)
CV (%) Geometric Mean	323.0	227.4
Median	108.757	115.734
Min, Max	9.98, 5021.60	10.99, 1801.26
Change from baseline		
n	80	22
Mean (SD)	-94.898 (463.393)	-0.596 (132.058)
SE	51.809	28.155
Median	-3.975	-1.015
Min, Max	-2485.85, 726.46	-322.38, 360.27

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Table 12.3
Cardiac Biomarkers - NT-proBNP (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Cardiac Subpopulation: No

Subgroup Visit	Vutrisiran (HELIOS-A) (N=82)	Patisiran (HELIOS-A) (N=28)
Week 72		
Actual Value		
n	80	24
Mean (SD)	597.919 (1321.832)	581.701 (1793.372)
SE	147.785	366.071
Geometric Mean (SEM)	147.871 (27.012)	128.702 (43.285)
CV (%) Geometric Mean	366.5	375.5
Median	118.736	97.763
Min, Max	6.00, 8107.13	4.99, 8937.44
Change from baseline		
n	80	24
Mean (SD)	69.903 (783.705)	222.655 (1184.083)
SE	87.621	241.700
Median	-6.004	-0.507
Min, Max	-1111.67, 5402.75	-438.16, 5731.14

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Table 12.3
Cardiac Biomarkers - NT-proBNP (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Cardiac Subpopulation: No

Subgroup Visit	Vutrisiran (HELIOS-A) (N=82)	Patisiran (HELIOS-A) (N=28)
Month 18		
Actual Value		
n	78	25
Mean (SD)	532.163 (933.029)	606.580 (1601.123)
SE	105.645	320.225
Geometric Mean (SEM)	143.511 (26.774)	143.705 (47.100)
CV (%) Geometric Mean	375.5	369.7
Median	106.304	125.756
Min, Max	4.99, 3880.92	4.99, 7947.47
Change from baseline		
n	78	25
Mean (SD)	6.998 (498.948)	193.878 (972.664)
SE	56.495	194.533
Median	-3.975	-7.950
Min, Max	-1725.40, 2123.55	-425.13, 4741.16

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Table 12.3
Cardiac Biomarkers - NT-proBNP (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Weight (kg): <65

Subgroup Visit	Vutrisiran (HELIOS-A) (N=46)	Patisiran (HELIOS-A) (N=15)
Baseline		
n	46	15
Mean (SD)	1722.965 (3122.372)	924.609 (1334.082)
SE	460.369	344.458
Geometric Mean (SEM)	545.120 (132.510)	221.815 (118.527)
CV (%) Geometric Mean	376.2	845.3
Median	603.745	183.601
Min, Max	14.97, 18755.00	7.02, 4200.25
Week 12		
Actual Value		
n	44	14
Mean (SD)	1904.315 (4742.431)	547.011 (781.001)
SE	714.948	208.731
Geometric Mean (SEM)	495.584 (122.807)	139.634 (73.071)
CV (%) Geometric Mean	372.9	672.6
Median	463.528	92.816
Min, Max	20.97, 30496.62	4.99, 2250.32
Change from baseline		
n	44	14
Mean (SD)	288.874 (1908.012)	-143.624 (354.133)
SE	287.644	94.646
Median	-17.506	-34.927
Min, Max	-1699.43, 11741.61	-955.98, 239.50

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Table 12.3
Cardiac Biomarkers - NT-proBNP (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Weight (kg): <65

Subgroup Visit	Vutrisiran (HELIOS-A) (N=46)	Patisiran (HELIOS-A) (N=15)
Week 24		
Actual Value		
n	45	13
Mean (SD)	1706.564 (3894.624)	1005.284 (1826.858)
SE	580.576	506.679
Geometric Mean (SEM)	462.211 (112.557)	158.585 (94.905)
CV (%) Geometric Mean	366.3	1020.8
Median	341.325	120.766
Min, Max	21.99, 24392.27	7.95, 5480.64
Change from baseline		
n	45	13
Mean (SD)	113.938 (1186.901)	182.001 (488.079)
SE	176.933	135.369
Median	-4.990	0.930
Min, Max	-1970.90, 5637.27	-226.56, 1280.39

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Table 12.3
Cardiac Biomarkers - NT-proBNP (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Weight (kg): <65

Subgroup Visit	Vutrisiran (HELIOS-A) (N=46)	Patisiran (HELIOS-A) (N=15)
Month 9		
Actual Value		
n	44	14
Mean (SD)	1084.606 (1483.267)	1493.832 (2889.470)
SE	223.611	772.243
Geometric Mean (SEM)	422.266 (96.885)	278.568 (147.510)
CV (%) Geometric Mean	302.3	704.9
Median	479.512	173.664
Min, Max	18.94, 7455.52	21.99, 10173.86
Change from baseline		
n	44	14
Mean (SD)	-117.966 (797.076)	533.830 (1708.054)
SE	120.164	456.497
Median	-18.436	21.016
Min, Max	-4190.27, 1416.04	-950.06, 5973.60

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Table 12.3
Cardiac Biomarkers - NT-proBNP (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Weight (kg): <65

Subgroup Visit	Vutrisiran (HELIOS-A) (N=46)	Patisiran (HELIOS-A) (N=15)
Week 48		
Actual Value		
n	42	14
Mean (SD)	1162.505 (1587.924)	1061.855 (1782.344)
SE	245.022	476.352
Geometric Mean (SEM)	430.152 (103.354)	217.725 (116.767)
CV (%) Geometric Mean	320.9	742.1
Median	381.199	123.261
Min, Max	18.94, 7502.37	12.94, 5318.95
Change from baseline		
n	42	14
Mean (SD)	-73.761 (1212.713)	126.233 (686.204)
SE	187.126	183.396
Median	-2.030	12.939
Min, Max	-4292.10, 5112.34	-1159.62, 2112.64

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Table 12.3
Cardiac Biomarkers - NT-proBNP (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Weight (kg): <65

Subgroup Visit	Vutrisiran (HELIOS-A) (N=46)	Patisiran (HELIOS-A) (N=15)
Week 60		
Actual Value		
n	44	13
Mean (SD)	1076.142 (1396.315)	869.737 (1797.568)
SE	210.502	498.556
Geometric Mean (SEM)	403.015 (94.090)	165.028 (90.313)
CV (%) Geometric Mean	316.3	693.4
Median	368.725	107.742
Min, Max	17.93, 4942.69	10.99, 6561.36
Change from baseline		
n	44	13
Mean (SD)	-126.430 (919.063)	82.527 (783.656)
SE	138.554	217.347
Median	-2.495	-8.034
Min, Max	-4326.01, 1489.87	-1281.32, 2361.11

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Table 12.3
Cardiac Biomarkers - NT-proBNP (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Weight (kg): <65

Subgroup Visit	Vutrisiran (HELIOS-A) (N=46)	Patisiran (HELIOS-A) (N=15)
Week 72		
Actual Value		
n	44	14
Mean (SD)	1341.920 (2108.576)	1182.246 (2503.839)
SE	317.880	669.179
Geometric Mean (SEM)	450.884 (104.938)	185.476 (101.251)
CV (%) Geometric Mean	313.7	799.0
Median	377.732	97.763
Min, Max	20.97, 8107.13	7.95, 8937.44
Change from baseline		
n	44	14
Mean (SD)	139.348 (1433.658)	313.054 (1604.720)
SE	216.132	428.879
Median	-27.443	-13.996
Min, Max	-4150.36, 5487.58	-1215.52, 5731.14

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Table 12.3
Cardiac Biomarkers - NT-proBNP (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Weight (kg): <65

Subgroup Visit	Vutrisiran (HELIOS-A) (N=46)	Patisiran (HELIOS-A) (N=15)
Month 18		
Actual Value		
n	42	15
Mean (SD)	1370.632 (2134.383)	1218.941 (2300.213)
SE	329.342	593.912
Geometric Mean (SEM)	390.201 (104.538)	221.448 (112.548)
CV (%) Geometric Mean	440.2	686.8
Median	337.815	125.756
Min, Max	12.94, 9582.12	17.00, 7947.47
Change from baseline		
n	42	15
Mean (SD)	156.748 (1573.670)	294.332 (1350.210)
SE	242.823	348.623
Median	-37.930	9.979
Min, Max	-4300.05, 7674.05	-1591.69, 4741.16

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Table 12.3
Cardiac Biomarkers - NT-proBNP (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Weight (kg): ≥65

Subgroup Visit	Vutrisiran (HELIOS-A) (N=76)	Patisiran (HELIOS-A) (N=27)
Baseline		
n	76	27
Mean (SD)	578.913 (1048.027)	1348.193 (2813.529)
SE	120.217	541.464
Geometric Mean (SEM)	179.638 (33.290)	386.981 (130.257)
CV (%) Geometric Mean	355.0	450.6
Median	167.153	427.079
Min, Max	4.99, 7052.38	4.99, 14324.21
Week 12		
Actual Value		
n	74	24
Mean (SD)	579.744 (985.281)	1402.121 (3281.220)
SE	114.537	669.776
Geometric Mean (SEM)	185.475 (35.903)	315.264 (121.019)
CV (%) Geometric Mean	387.3	577.5
Median	198.613	420.101
Min, Max	4.99, 6818.79	4.99, 15851.04
Change from baseline		
n	74	24
Mean (SD)	7.006 (280.966)	53.261 (545.964)
SE	32.662	111.444
Median	2.030	-6.977
Min, Max	-1201.49, 1223.39	-1200.47, 1526.83

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Table 12.3
Cardiac Biomarkers - NT-proBNP (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Weight (kg): ≥65

Subgroup Visit	Vutrisiran (HELIOS-A) (N=76)	Patisiran (HELIOS-A) (N=27)
Week 24		
Actual Value		
n	73	25
Mean (SD)	570.975 (1121.278)	1328.913 (2951.408)
SE	131.236	590.282
Geometric Mean (SEM)	174.580 (33.748)	325.359 (116.220)
CV (%) Geometric Mean	378.1	482.6
Median	135.735	311.387
Min, Max	4.99, 8382.58	4.99, 13526.89
Change from baseline		
n	73	25
Mean (SD)	12.796 (320.264)	5.426 (670.567)
SE	37.484	134.113
Median	2.960	-15.984
Min, Max	-953.02, 1491.90	-1187.53, 2801.21

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Table 12.3
Cardiac Biomarkers - NT-proBNP (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Weight (kg): ≥65

Subgroup Visit	Vutrisiran (HELIOS-A) (N=76)	Patisiran (HELIOS-A) (N=27)
Month 9		
Actual Value		
n	69	24
Mean (SD)	538.180 (866.788)	1073.771 (2681.924)
SE	104.349	547.446
Geometric Mean (SEM)	183.685 (33.963)	302.340 (103.261)
CV (%) Geometric Mean	309.5	392.9
Median	163.643	382.214
Min, Max	10.99, 4942.69	4.99, 13397.16
Change from baseline		
n	69	24
Mean (SD)	8.328 (487.360)	291.981 (1828.126)
SE	58.671	373.165
Median	7.950	1.480
Min, Max	-2109.68, 1722.44	-1179.50, 8722.89

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Alnylam Pharmaceuticals Inc.
ALN-TTRSC02-002

Table 12.3
Cardiac Biomarkers - NT-proBNP (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Weight (kg): ≥65

Subgroup Visit	Vutrisiran (HELIOS-A) (N=76)	Patisiran (HELIOS-A) (N=27)
Week 48		
Actual Value		
n	72	25
Mean (SD)	608.056 (1024.190)	1567.190 (3732.515)
SE	120.702	746.503
Geometric Mean (SEM)	179.106 (35.896)	340.284 (120.212)
CV (%) Geometric Mean	412.7	465.3
Median	183.601	312.317
Min, Max	6.00, 5949.67	4.99, 15523.75
Change from baseline		
n	72	25
Mean (SD)	26.046 (513.324)	243.704 (1477.501)
SE	60.496	295.500
Median	-5.539	-6.004
Min, Max	-1729.46, 2879.02	-724.43, 7155.13

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

Alnylam Pharmaceuticals Inc.
ALN-TTRSC02-002

Table 12.3
Cardiac Biomarkers - NT-proBNP (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Weight (kg): ≥65

Subgroup Visit	Vutrisiran (HELIOS-A) (N=76)	Patisiran (HELIOS-A) (N=27)
Week 60		
Actual Value		
n	74	22
Mean (SD)	489.535 (778.002)	1050.721 (2606.742)
SE	90.441	555.759
Geometric Mean (SEM)	170.695 (31.213)	337.973 (100.305)
CV (%) Geometric Mean	329.8	243.8
Median	159.161	322.339
Min, Max	9.98, 5021.60	28.92, 12454.12
Change from baseline		
n	74	22
Mean (SD)	-68.384 (387.148)	-155.632 (548.943)
SE	45.005	117.035
Median	-3.975	-5.497
Min, Max	-2030.78, 774.41	-1870.10, 450.08

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

Alnylam Pharmaceuticals Inc.
ALN-TTRSC02-002

Table 12.3
Cardiac Biomarkers - NT-proBNP (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Weight (kg): ≥65

Subgroup Visit	Vutrisiran (HELIOS-A) (N=76)	Patisiran (HELIOS-A) (N=27)
Week 72		
Actual Value		
n	74	23
Mean (SD)	529.978 (951.772)	1027.382 (2815.053)
SE	110.641	586.979
Geometric Mean (SEM)	157.781 (30.689)	271.882 (93.182)
CV (%) Geometric Mean	392.9	372.9
Median	153.706	342.255
Min, Max	4.99, 6525.42	4.99, 13774.34
Change from baseline		
n	74	23
Mean (SD)	52.191 (725.930)	-126.737 (415.302)
SE	84.388	86.596
Median	4.990	-1.015
Min, Max	-1111.67, 5402.75	-1682.44, 343.27

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

Alnylam Pharmaceuticals Inc.
ALN-TTRSC02-002

Table 12.3
Cardiac Biomarkers - NT-proBNP (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Weight (kg): ≥65

Subgroup Visit	Vutrisiran (HELIOS-A) (N=76)	Patisiran (HELIOS-A) (N=27)
Month 18		
Actual Value		
n	72	23
Mean (SD)	530.077 (816.194)	1125.833 (3073.854)
SE	96.189	640.943
Geometric Mean (SEM)	165.673 (32.599)	287.800 (100.812)
CV (%) Geometric Mean	390.4	397.6
Median	180.134	329.316
Min, Max	4.99, 3880.92	4.99, 15039.76
Change from baseline		
n	72	23
Mean (SD)	54.125 (522.228)	-28.287 (522.937)
SE	61.545	109.040
Median	2.960	-7.950
Min, Max	-1256.46, 2459.89	-1911.03, 947.01

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

Troponin T

Alnylam Pharmaceuticals Inc.
ALN-TTRSC02-002

Table 13.2
Cardiac Biomarkers - Troponin T (ng/L): Change from Baseline to Month 18, MMRM Model
Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A) Subgroup Analysis
mITT Population

Subgroup Visit	LS Mean (95% CI) Vutrisiran (HELIOS-A) (N=122)	LS Mean (95% CI) Patisiran (HELIOS-A) (N=42)	LS Mean Difference (Vutrisiran-Patisiran) (95% CI), p-value	Standardized Effect Size (95% CI)
Age (years)				
<65	76	30		
Week 12	-0.46 (-2.55, 1.64)	1.89 (-1.45, 5.23)	-2.35 (-6.28, 1.58), 0.2389	-0.30 (-0.72, 0.13)
Week 24	0.11 (-2.01, 2.24)	1.27 (-2.14, 4.68)	-1.16 (-5.16, 2.85), 0.5690	-0.16 (-0.59, 0.27)
Month 9	0.63 (-2.15, 3.41)	6.82 (2.18, 11.46)	-6.19 (-11.59, -0.79), 0.0249	-0.47 (-0.90, -0.03)
Week 48	-0.37 (-3.57, 2.84)	4.91 (-0.53, 10.35)	-5.28 (-11.59, 1.03), 0.1003	-0.55 (-0.98, -0.12)
Week 60	0.44 (-2.02, 2.90)	0.45 (-3.63, 4.53)	-0.01 (-4.76, 4.74), 0.9961	-0.00 (-0.44, 0.44)
Week 72	1.39 (-3.24, 6.03)	8.18 (0.06, 16.30)	-6.79 (-16.13, 2.55), 0.1527	-0.51 (-0.95, -0.06)
Month 18	1.74 (-2.31, 5.79)	5.18 (-1.83, 12.20)	-3.45 (-11.54, 4.65), 0.3986	-0.23 (-0.65, 0.20)
≥65	44	9		
Week 12	-1.48 (-4.08, 1.13)	7.88 (1.96, 13.80)	-9.36 (-15.80, -2.91), 0.0047	-0.89 (-1.66, -0.13)
Week 24	-0.90 (-3.54, 1.74)	7.26 (1.30, 13.22)	-8.16 (-14.67, -1.66), 0.0141	-0.59 (-1.34, 0.17)
Month 9	-0.39 (-3.57, 2.79)	12.81 (6.08, 19.54)	-13.20 (-20.62, -5.77), 0.0006	-1.04 (-1.82, -0.27)
Week 48	-1.38 (-4.94, 2.18)	10.90 (3.62, 18.19)	-12.29 (-20.38, -4.19), 0.0031	-0.48 (-1.19, 0.23)
Week 60	-0.58 (-3.48, 2.33)	6.44 (0.10, 12.78)	-7.02 (-13.98, -0.06), 0.0480	-0.54 (-1.29, 0.21)
Week 72	0.37 (-4.51, 5.26)	14.17 (4.74, 23.61)	-13.80 (-24.41, -3.19), 0.0111	-0.47 (-1.22, 0.28)
Month 18	0.72 (-3.60, 5.05)	11.17 (2.70, 19.65)	-10.45 (-19.96, -0.95), 0.0313	-0.79 (-1.60, 0.02)
p-value of Treatment*Age	0.0541			

LS estimates and p-value derived from mixed-effects model for repeated measures (MMRM), controlling for categorical factors (treatment, visit), the subgroup variable, continuous covariate (baseline value), and interaction (treatment by visit, treatment by subgroup).
Standardized effect size (d) = LS mean difference/estimated pooled standard deviation with the small sample bias correction.

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

Alnylam Pharmaceuticals Inc.
ALN-TTRSC02-002

Table 13.2
Cardiac Biomarkers - Troponin T (ng/L): Change from Baseline to Month 18, MMRM Model
Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A) Subgroup Analysis
mITT Population

Subgroup Visit	LS Mean (95% CI) Vutrisiran (HELIOS-A) (N=122)	LS Mean (95% CI) Patisiran (HELIOS-A) (N=42)	LS Mean Difference (Vutrisiran-Patisiran) (95% CI), p-value	Standardized Effect Size (95% CI)
Sex				
Male	77	24		
Week 12	-1.21 (-3.28, 0.86)	3.19 (-0.57, 6.95)	-4.40 (-8.70, -0.09), 0.0453	-0.42 (-0.89, 0.05)
Week 24	-0.63 (-2.74, 1.48)	2.56 (-1.27, 6.39)	-3.19 (-7.58, 1.20), 0.1529	-0.28 (-0.75, 0.18)
Month 9	-0.12 (-2.88, 2.64)	8.07 (3.13, 13.02)	-8.19 (-13.86, -2.52), 0.0049	-0.73 (-1.21, -0.25)
Week 48	-1.12 (-4.36, 2.13)	6.22 (0.42, 12.02)	-7.34 (-13.99, -0.68), 0.0310	-0.36 (-0.82, 0.11)
Week 60	-0.31 (-2.78, 2.16)	1.77 (-2.71, 6.24)	-2.08 (-7.20, 3.04), 0.4243	-0.16 (-0.64, 0.31)
Week 72	0.64 (-4.04, 5.32)	9.46 (1.07, 17.85)	-8.82 (-18.44, 0.80), 0.0719	-0.37 (-0.85, 0.11)
Month 18	0.99 (-3.10, 5.08)	6.50 (-0.79, 13.80)	-5.52 (-13.89, 2.86), 0.1934	-0.34 (-0.83, 0.14)
Female	43	15		
Week 12	-0.05 (-2.76, 2.66)	3.32 (-1.25, 7.88)	-3.37 (-8.64, 1.91), 0.2093	-0.60 (-1.21, 0.00)
Week 24	0.53 (-2.22, 3.27)	2.69 (-1.96, 7.34)	-2.16 (-7.53, 3.21), 0.4276	-0.30 (-0.92, 0.31)
Month 9	1.04 (-2.22, 4.30)	8.20 (2.62, 13.78)	-7.17 (-13.60, -0.73), 0.0293	-0.45 (-1.05, 0.16)
Week 48	0.04 (-3.64, 3.72)	6.35 (0.01, 12.69)	-6.31 (-13.62, 1.00), 0.0905	-0.78 (-1.37, -0.18)
Week 60	0.85 (-2.17, 3.86)	1.89 (-3.28, 7.07)	-1.05 (-7.01, 4.92), 0.7292	-0.14 (-0.76, 0.47)
Week 72	1.80 (-3.19, 6.78)	9.59 (0.82, 18.35)	-7.79 (-17.86, 2.28), 0.1283	-0.69 (-1.32, -0.06)
Month 18	2.15 (-2.29, 6.58)	6.63 (-1.10, 14.37)	-4.49 (-13.39, 4.41), 0.3193	-0.38 (-0.96, 0.21)
p-value of Treatment*Sex	0.7502			

LS estimates and p-value derived from mixed-effects model for repeated measures (MMRM), controlling for categorical factors (treatment, visit), the subgroup variable, continuous covariate (baseline value), and interaction (treatment by visit, treatment by subgroup).
Standardized effect size (d) = LS mean difference/estimated pooled standard deviation with the small sample bias correction.

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

Alnylam Pharmaceuticals Inc.
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Table 13.2
Cardiac Biomarkers - Troponin T (ng/L): Change from Baseline to Month 18, MMRM Model
Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A) Subgroup Analysis
mITT Population

Subgroup Visit	LS Mean (95% CI) Vutrisiran (HELIOS-A) (N=122)	LS Mean (95% CI) Patisiran (HELIOS-A) (N=42)	LS Mean Difference (Vutrisiran-Patisiran) (95% CI), p-value	Standardized Effect Size (95% CI)
Race				
White	84	26		
Week 12	0.20 (-1.81, 2.21)	3.33 (-0.21, 6.87)	-3.13 (-7.20, 0.93), 0.1301	-0.50 (-0.96, -0.05)
Week 24	0.77 (-1.29, 2.83)	2.71 (-0.91, 6.33)	-1.94 (-6.10, 2.22), 0.3582	-0.33 (-0.78, 0.12)
Month 9	1.29 (-1.40, 3.98)	8.21 (3.48, 12.95)	-6.93 (-12.37, -1.48), 0.0130	-0.56 (-1.01, -0.11)
Week 48	0.29 (-2.90, 3.49)	6.37 (0.74, 11.99)	-6.07 (-12.54, 0.39), 0.0654	-0.70 (-1.15, -0.25)
Week 60	1.10 (-1.32, 3.52)	1.91 (-2.39, 6.20)	-0.81 (-5.73, 4.12), 0.7468	-0.09 (-0.54, 0.36)
Week 72	2.06 (-2.59, 6.70)	9.63 (1.36, 17.90)	-7.58 (-17.06, 1.91), 0.1163	-0.55 (-1.02, -0.09)
Month 18	2.39 (-1.64, 6.43)	6.64 (-0.52, 13.80)	-4.25 (-12.47, 3.97), 0.3061	-0.30 (-0.74, 0.15)
All Other Races	36	13		
Week 12	-2.92 (-5.78, -0.06)	2.83 (-2.05, 7.71)	-5.75 (-11.38, -0.13), 0.0451	-0.44 (-1.07, 0.19)
Week 24	-2.35 (-5.25, 0.55)	2.21 (-2.77, 7.19)	-4.56 (-10.29, 1.17), 0.1180	-0.29 (-0.96, 0.38)
Month 9	-1.84 (-5.21, 1.53)	7.71 (1.90, 13.52)	-9.55 (-16.24, -2.86), 0.0054	-0.67 (-1.35, 0.02)
Week 48	-2.83 (-6.61, 0.95)	5.87 (-0.69, 12.42)	-8.70 (-16.24, -1.15), 0.0241	-0.31 (-0.96, 0.34)
Week 60	-2.02 (-5.18, 1.13)	1.40 (-4.07, 6.88)	-3.43 (-9.72, 2.86), 0.2839	-0.23 (-0.90, 0.44)
Week 72	-1.07 (-6.12, 3.99)	9.13 (0.21, 18.05)	-10.20 (-20.43, 0.03), 0.0507	-0.33 (-1.00, 0.34)
Month 18	-0.73 (-5.24, 3.78)	6.14 (-1.74, 14.02)	-6.87 (-15.93, 2.18), 0.1354	-0.45 (-1.15, 0.25)
p-value of Treatment*Race	0.4291			

LS estimates and p-value derived from mixed-effects model for repeated measures (MMRM), controlling for categorical factors (treatment, visit), the subgroup variable, continuous covariate (baseline value), and interaction (treatment by visit, treatment by subgroup).
Standardized effect size (d) = LS mean difference/estimated pooled standard deviation with the small sample bias correction.

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

Alnylam Pharmaceuticals Inc.
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Table 13.2
Cardiac Biomarkers - Troponin T (ng/L): Change from Baseline to Month 18, MMRM Model
Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A) Subgroup Analysis
mITT Population

Subgroup Visit	LS Mean (95% CI) Vutrisiran (HELIOS-A) (N=122)	LS Mean (95% CI) Patisiran (HELIOS-A) (N=42)	LS Mean Difference (Vutrisiran-Patisiran) (95% CI), p-value	Standardized Effect Size (95% CI)
Region				
North America	27	8		
Week 12	0.21 (-3.15, 3.57)	7.02 (0.79, 13.24)	-6.81 (-14.01, 0.39), 0.0638	-0.71 (-1.50, 0.08)
Week 24	0.79 (-2.59, 4.17)	6.39 (0.16, 12.62)	-5.60 (-12.81, 1.62), 0.1274	-0.42 (-1.21, 0.36)
Month 9	1.30 (-2.51, 5.12)	11.93 (4.94, 18.92)	-10.62 (-18.70, -2.55), 0.0102	-0.93 (-1.78, -0.07)
Week 48	0.31 (-3.83, 4.44)	10.04 (2.50, 17.58)	-9.74 (-18.44, -1.03), 0.0285	-0.33 (-1.11, 0.45)
Week 60	1.11 (-2.49, 4.71)	5.58 (-1.06, 12.23)	-4.47 (-12.15, 3.20), 0.2517	-0.42 (-1.24, 0.40)
Week 72	2.05 (-3.24, 7.35)	13.24 (3.69, 22.79)	-11.19 (-22.19, -0.18), 0.0463	-0.32 (-1.26, 0.62)
Month 18	2.40 (-2.39, 7.20)	10.33 (1.65, 19.01)	-7.93 (-17.93, 2.08), 0.1196	-0.77 (-1.66, 0.12)
Western Europe	40	18		
Week 12	-0.47 (-3.27, 2.33)	3.07 (-1.11, 7.25)	-3.54 (-8.56, 1.48), 0.1654	-0.56 (-1.13, 0.01)
Week 24	0.11 (-2.71, 2.92)	2.44 (-1.81, 6.69)	-2.33 (-7.42, 2.75), 0.3663	-0.37 (-0.97, 0.22)
Month 9	0.62 (-2.71, 3.95)	7.98 (2.73, 13.23)	-7.36 (-13.56, -1.15), 0.0204	-0.89 (-1.48, -0.31)
Week 48	-0.38 (-4.08, 3.32)	6.09 (0.11, 12.08)	-6.47 (-13.50, 0.56), 0.0709	-0.69 (-1.27, -0.12)
Week 60	0.43 (-2.66, 3.51)	1.63 (-3.17, 6.44)	-1.21 (-6.90, 4.49), 0.6764	-0.13 (-0.70, 0.44)
Week 72	1.37 (-3.61, 6.34)	9.29 (0.82, 17.76)	-7.92 (-17.74, 1.90), 0.1128	-0.62 (-1.20, -0.03)
Month 18	1.72 (-2.72, 6.15)	6.38 (-1.05, 13.80)	-4.66 (-13.30, 3.98), 0.2869	-0.49 (-1.06, 0.08)

LS estimates and p-value derived from mixed-effects model for repeated measures (MMRM), controlling for categorical factors (treatment, visit), the subgroup variable, continuous covariate (baseline value), and interaction (treatment by visit, treatment by subgroup).
Standardized effect size (d) = LS mean difference/estimated pooled standard deviation with the small sample bias correction.

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

Alnylam Pharmaceuticals Inc.
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Table 13.2
Cardiac Biomarkers - Troponin T (ng/L): Change from Baseline to Month 18, MMRM Model
Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A) Subgroup Analysis
mITT Population

Subgroup Visit	LS Mean (95% CI) Vutrisiran (HELIOS-A) (N=122)	LS Mean (95% CI) Patisiran (HELIOS-A) (N=42)	LS Mean Difference (Vutrisiran-Patisiran) (95% CI), p-value	Standardized Effect Size (95% CI)
Rest of World	53	13		
Week 12	-1.49 (-3.91, 0.93)	1.05 (-3.78, 5.88)	-2.54 (-7.93, 2.86), 0.3549	-0.25 (-0.87, 0.38)
Week 24	-0.91 (-3.34, 1.53)	0.42 (-4.41, 5.25)	-1.33 (-6.73, 4.08), 0.6286	-0.13 (-0.73, 0.47)
Month 9	-0.40 (-3.41, 2.62)	5.96 (0.18, 11.74)	-6.35 (-12.87, 0.16), 0.0559	-0.38 (-1.00, 0.25)
Week 48	-1.39 (-4.82, 2.03)	4.07 (-2.37, 10.51)	-5.47 (-12.76, 1.82), 0.1408	-0.43 (-1.03, 0.18)
Week 60	-0.59 (-3.33, 2.16)	-0.39 (-5.74, 4.97)	-0.20 (-6.22, 5.81), 0.9474	-0.02 (-0.64, 0.60)
Week 72	0.35 (-4.42, 5.13)	7.27 (-1.54, 16.08)	-6.92 (-16.93, 3.10), 0.1744	-0.43 (-1.03, 0.18)
Month 18	0.70 (-3.51, 4.92)	4.36 (-3.43, 12.15)	-3.65 (-12.51, 5.20), 0.4145	-0.19 (-0.79, 0.42)
p-value of Treatment*Region	0.6182			

LS estimates and p-value derived from mixed-effects model for repeated measures (MMRM), controlling for categorical factors (treatment, visit), the subgroup variable, continuous covariate (baseline value), and interaction (treatment by visit, treatment by subgroup).
Standardized effect size (d) = LS mean difference/estimated pooled standard deviation with the small sample bias correction.

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

Alnylam Pharmaceuticals Inc.
ALN-TTRSC02-002

Table 13.2
Cardiac Biomarkers - Troponin T (ng/L): Change from Baseline to Month 18, MMRM Model
Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A) Subgroup Analysis
mITT Population

Subgroup Visit	LS Mean (95% CI) Vutrisiran (HELIOS-A) (N=122)	LS Mean (95% CI) Patisiran (HELIOS-A) (N=42)	LS Mean Difference (Vutrisiran-Patisiran) (95% CI), p-value	Standardized Effect Size (95% CI)
Baseline NIS				
<50	78	26		
Week 12	0.37 (-1.74, 2.49)	2.65 (-0.88, 6.19)	-2.28 (-6.44, 1.87), 0.2790	-0.31 (-0.76, 0.14)
Week 24	0.95 (-1.22, 3.13)	2.06 (-1.57, 5.68)	-1.10 (-5.36, 3.15), 0.6096	-0.12 (-0.57, 0.32)
Month 9	1.46 (-1.32, 4.24)	7.56 (2.79, 12.32)	-6.10 (-11.64, -0.57), 0.0310	-0.70 (-1.17, -0.23)
Week 48	0.46 (-2.80, 3.73)	5.70 (0.06, 11.34)	-5.24 (-11.77, 1.29), 0.1153	-0.29 (-0.73, 0.16)
Week 60	1.27 (-1.25, 3.79)	1.25 (-3.07, 5.57)	0.02 (-5.00, 5.04), 0.9928	0.00 (-0.46, 0.47)
Week 72	2.21 (-2.49, 6.90)	8.96 (0.68, 17.24)	-6.75 (-16.28, 2.78), 0.1632	-0.32 (-0.79, 0.16)
Month 18	2.56 (-1.59, 6.71)	6.09 (-1.17, 13.36)	-3.53 (-11.91, 4.85), 0.4039	-0.38 (-0.84, 0.08)
≥50	42	13		
Week 12	-2.76 (-5.45, -0.07)	4.13 (-0.69, 8.95)	-6.89 (-12.38, -1.41), 0.0141	-0.61 (-1.25, 0.03)
Week 24	-2.18 (-4.91, 0.55)	3.53 (-1.41, 8.48)	-5.71 (-11.33, -0.10), 0.0463	-0.50 (-1.18, 0.19)
Month 9	-1.68 (-4.91, 1.56)	9.04 (3.27, 14.80)	-10.71 (-17.29, -4.13), 0.0016	-0.57 (-1.22, 0.08)
Week 48	-2.67 (-6.33, 0.99)	7.18 (0.66, 13.70)	-9.85 (-17.30, -2.40), 0.0098	-0.72 (-1.37, -0.07)
Week 60	-1.86 (-4.88, 1.15)	2.73 (-2.69, 8.14)	-4.59 (-10.76, 1.58), 0.1441	-0.34 (-0.98, 0.30)
Week 72	-0.93 (-5.91, 4.06)	10.44 (1.52, 19.36)	-11.36 (-21.56, -1.17), 0.0292	-0.61 (-1.25, 0.03)
Month 18	-0.57 (-5.04, 3.90)	7.57 (-0.38, 15.53)	-8.14 (-17.24, 0.96), 0.0790	-0.37 (-1.01, 0.27)
p-value of Treatment*Baseline NIS	0.1640			

LS estimates and p-value derived from mixed-effects model for repeated measures (MMRM), controlling for categorical factors (treatment, visit), the subgroup variable, continuous covariate (baseline value), and interaction (treatment by visit, treatment by subgroup).
Standardized effect size (d) = LS mean difference/estimated pooled standard deviation with the small sample bias correction.

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Table 13.2
Cardiac Biomarkers - Troponin T (ng/L): Change from Baseline to Month 18, MMRM Model
Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A) Subgroup Analysis
mITT Population

Subgroup Visit	LS Mean (95% CI) Vutrisiran (HELIOS-A) (N=122)	LS Mean (95% CI) Patisiran (HELIOS-A) (N=42)	LS Mean Difference (Vutrisiran-Patisiran) (95% CI), p-value	Standardized Effect Size (95% CI)
Previous Tetramer Stabilizer Use				
Yes	74	31		
Week 12	-0.44 (-2.56, 1.67)	2.97 (-0.37, 6.30)	-3.41 (-7.36, 0.53), 0.0894	-0.38 (-0.81, 0.05)
Week 24	0.13 (-2.02, 2.28)	2.33 (-1.10, 5.76)	-2.20 (-6.25, 1.84), 0.2832	-0.25 (-0.68, 0.19)
Month 9	0.64 (-2.15, 3.43)	7.86 (3.23, 12.49)	-7.22 (-12.62, -1.82), 0.0091	-0.52 (-0.95, -0.09)
Week 48	-0.35 (-3.61, 2.92)	6.00 (0.48, 11.51)	-6.35 (-12.75, 0.06), 0.0523	-0.57 (-1.00, -0.14)
Week 60	0.46 (-2.05, 2.96)	1.55 (-2.57, 5.67)	-1.09 (-5.91, 3.73), 0.6552	-0.10 (-0.53, 0.33)
Week 72	1.41 (-3.28, 6.10)	9.24 (1.03, 17.44)	-7.83 (-17.28, 1.63), 0.1037	-0.53 (-0.97, -0.09)
Month 18	1.75 (-2.34, 5.85)	6.26 (-0.82, 13.33)	-4.50 (-12.67, 3.67), 0.2753	-0.29 (-0.71, 0.14)
No	46	8		
Week 12	-1.40 (-3.99, 1.19)	4.37 (-1.91, 10.65)	-5.78 (-12.61, 1.06), 0.0974	-0.64 (-1.39, 0.11)
Week 24	-0.83 (-3.46, 1.80)	3.74 (-2.57, 10.04)	-4.57 (-11.45, 2.31), 0.1918	-0.39 (-1.13, 0.36)
Month 9	-0.32 (-3.48, 2.85)	9.27 (2.21, 16.32)	-9.58 (-17.36, -1.81), 0.0160	-0.86 (-1.73, -0.00)
Week 48	-1.31 (-4.89, 2.28)	7.40 (-0.24, 15.05)	-8.71 (-17.19, -0.23), 0.0442	-0.35 (-1.09, 0.40)
Week 60	-0.50 (-3.41, 2.41)	2.95 (-3.80, 9.69)	-3.45 (-10.84, 3.94), 0.3579	-0.32 (-1.16, 0.52)
Week 72	0.45 (-4.47, 5.37)	10.64 (0.93, 20.34)	-10.19 (-21.09, 0.72), 0.0669	-0.36 (-1.20, 0.48)
Month 18	0.79 (-3.55, 5.14)	7.66 (-1.12, 16.44)	-6.86 (-16.69, 2.96), 0.1692	-0.56 (-1.41, 0.28)
p-value of Treatment*Previous Tetramer Stabilizer Use	0.5348			

LS estimates and p-value derived from mixed-effects model for repeated measures (MMRM), controlling for categorical factors (treatment, visit), the subgroup variable, continuous covariate (baseline value), and interaction (treatment by visit, treatment by subgroup).
Standardized effect size (d) = LS mean difference/estimated pooled standard deviation with the small sample bias correction.

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Table 13.2
Cardiac Biomarkers - Troponin T (ng/L): Change from Baseline to Month 18, MMRM Model
Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A) Subgroup Analysis
mITT Population

Subgroup Visit	LS Mean (95% CI) Vutrisiran (HELIOS-A) (N=122)	LS Mean (95% CI) Patisiran (HELIOS-A) (N=42)	LS Mean Difference (Vutrisiran-Patisiran) (95% CI), p-value	Standardized Effect Size (95% CI)
Genotype				
V30M	53	20		
Week 12	-0.00 (-2.46, 2.45)	0.77 (-3.21, 4.76)	-0.78 (-5.43, 3.87), 0.7410	-0.13 (-0.65, 0.39)
Week 24	0.56 (-1.92, 3.05)	0.13 (-3.93, 4.18)	0.44 (-4.29, 5.17), 0.8548	0.06 (-0.46, 0.59)
Month 9	1.08 (-1.96, 4.13)	5.65 (0.56, 10.75)	-4.57 (-10.48, 1.34), 0.1289	-0.57 (-1.10, -0.04)
Week 48	0.09 (-3.38, 3.57)	3.80 (-2.09, 9.69)	-3.71 (-10.53, 3.11), 0.2845	-0.46 (-0.98, 0.05)
Week 60	0.89 (-1.89, 3.67)	-0.66 (-5.29, 3.97)	1.55 (-3.82, 6.93), 0.5694	0.24 (-0.29, 0.77)
Week 72	1.86 (-2.99, 6.70)	7.04 (-1.41, 15.50)	-5.19 (-14.92, 4.54), 0.2935	-0.46 (-1.00, 0.07)
Month 18	2.20 (-2.11, 6.51)	4.18 (-3.27, 11.64)	-1.98 (-10.58, 6.62), 0.6479	-0.22 (-0.73, 0.29)
non-V30M	67	19		
Week 12	-1.49 (-3.66, 0.68)	5.94 (1.79, 10.08)	-7.43 (-12.11, -2.74), 0.0021	-0.68 (-1.20, -0.15)
Week 24	-0.92 (-3.13, 1.29)	5.29 (1.08, 9.49)	-6.21 (-10.96, -1.45), 0.0108	-0.52 (-1.04, 0.01)
Month 9	-0.40 (-3.22, 2.42)	10.82 (5.60, 16.03)	-11.22 (-17.15, -5.28), 0.0003	-0.69 (-1.24, -0.15)
Week 48	-1.39 (-4.67, 1.89)	8.96 (2.96, 14.97)	-10.36 (-17.20, -3.51), 0.0032	-0.48 (-1.00, 0.05)
Week 60	-0.59 (-3.13, 1.94)	4.50 (-0.27, 9.28)	-5.09 (-10.51, 0.32), 0.0648	-0.37 (-0.91, 0.16)
Week 72	0.37 (-4.33, 5.08)	12.21 (3.68, 20.73)	-11.83 (-21.57, -2.10), 0.0176	-0.46 (-1.00, 0.09)
Month 18	0.72 (-3.44, 4.88)	9.35 (1.82, 16.88)	-8.63 (-17.23, -0.03), 0.0493	-0.46 (-1.01, 0.08)
p-value of Treatment*Genotype	0.0334			

LS estimates and p-value derived from mixed-effects model for repeated measures (MMRM), controlling for categorical factors (treatment, visit), the subgroup variable, continuous covariate (baseline value), and interaction (treatment by visit, treatment by subgroup).
Standardized effect size (d) = LS mean difference/estimated pooled standard deviation with the small sample bias correction.

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Table 13.2
Cardiac Biomarkers - Troponin T (ng/L): Change from Baseline to Month 18, MMRM Model
Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A) Subgroup Analysis
mITT Population

Subgroup Visit	LS Mean (95% CI) Vutrisiran (HELIOS-A) (N=122)	LS Mean (95% CI) Patisiran (HELIOS-A) (N=42)	LS Mean Difference (Vutrisiran-Patisiran) (95% CI), p-value	Standardized Effect Size (95% CI)
FAP Stage				
I	84	29		
Week 12	0.23 (-1.82, 2.28)	2.11 (-1.28, 5.49)	-1.88 (-5.79, 2.04), 0.3455	-0.33 (-0.77, 0.10)
Week 24	0.80 (-1.29, 2.89)	1.54 (-1.89, 4.98)	-0.74 (-4.73, 3.24), 0.7136	-0.13 (-0.55, 0.29)
Month 9	1.32 (-1.41, 4.04)	7.03 (2.39, 11.67)	-5.71 (-11.06, -0.37), 0.0364	-0.46 (-0.89, -0.03)
Week 48	0.32 (-2.85, 3.50)	5.16 (-0.30, 10.61)	-4.83 (-11.12, 1.46), 0.1310	-0.57 (-1.00, -0.14)
Week 60	1.13 (-1.32, 3.58)	0.71 (-3.44, 4.86)	0.42 (-4.36, 5.20), 0.8621	0.05 (-0.38, 0.48)
Week 72	2.08 (-2.55, 6.71)	8.41 (0.25, 16.57)	-6.33 (-15.70, 3.04), 0.1834	-0.57 (-1.01, -0.12)
Month 18	2.43 (-1.64, 6.51)	5.52 (-1.60, 12.64)	-3.09 (-11.27, 5.10), 0.4546	-0.33 (-0.75, 0.10)
II&III	36	10		
Week 12	-3.08 (-5.98, -0.17)	6.31 (0.57, 12.06)	-9.39 (-15.65, -3.13), 0.0035	-0.67 (-1.38, 0.03)
Week 24	-2.51 (-5.44, 0.43)	5.75 (-0.12, 11.62)	-8.26 (-14.64, -1.87), 0.0115	-0.50 (-1.30, 0.31)
Month 9	-1.99 (-5.40, 1.42)	11.24 (4.68, 17.80)	-13.23 (-20.47, -5.99), 0.0004	-0.90 (-1.69, -0.12)
Week 48	-2.98 (-6.76, 0.80)	9.37 (2.19, 16.54)	-12.35 (-20.32, -4.38), 0.0025	-0.43 (-1.16, 0.29)
Week 60	-2.18 (-5.37, 1.01)	4.92 (-1.34, 11.18)	-7.09 (-13.96, -0.23), 0.0429	-0.45 (-1.21, 0.31)
Week 72	-1.22 (-6.28, 3.83)	12.62 (3.26, 21.98)	-13.84 (-24.38, -3.31), 0.0103	-0.41 (-1.17, 0.35)
Month 18	-0.87 (-5.42, 3.67)	9.73 (1.27, 18.18)	-10.60 (-20.08, -1.12), 0.0286	-0.44 (-1.24, 0.37)
p-value of Treatment*FAP Stage	0.0353			

LS estimates and p-value derived from mixed-effects model for repeated measures (MMRM), controlling for categorical factors (treatment, visit), the subgroup variable, continuous covariate (baseline value), and interaction (treatment by visit, treatment by subgroup).
Standardized effect size (d) = LS mean difference/estimated pooled standard deviation with the small sample bias correction.

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Table 13.2
Cardiac Biomarkers - Troponin T (ng/L): Change from Baseline to Month 18, MMRM Model
Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A) Subgroup Analysis
mITT Population

Subgroup Visit	LS Mean (95% CI) Vutrisiran (HELIOS-A) (N=122)	LS Mean (95% CI) Patisiran (HELIOS-A) (N=42)	LS Mean Difference (Vutrisiran-Patisiran) (95% CI), p-value	Standardized Effect Size (95% CI)
Cardiac Subpopulation				
Yes	39	13		
Week 12	-2.92 (-5.66, -0.17)	6.80 (1.92, 11.69)	-9.72 (-15.26, -4.18), 0.0007	-0.71 (-1.38, -0.03)
Week 24	-2.34 (-5.14, 0.45)	6.17 (1.20, 11.14)	-8.52 (-14.16, -2.88), 0.0033	-0.60 (-1.25, 0.05)
Month 9	-1.83 (-5.14, 1.49)	11.74 (5.85, 17.63)	-13.56 (-20.27, -6.85), 9.403E-05	-0.71 (-1.36, -0.05)
Week 48	-2.82 (-6.55, 0.91)	9.84 (3.23, 16.45)	-12.66 (-20.20, -5.11), 0.0011	-0.63 (-1.26, 0.00)
Week 60	-2.02 (-5.09, 1.04)	5.36 (-0.08, 10.80)	-7.38 (-13.57, -1.19), 0.0196	-0.45 (-1.07, 0.18)
Week 72	-1.06 (-6.09, 3.98)	13.14 (4.12, 22.15)	-14.19 (-24.48, -3.90), 0.0072	-0.43 (-1.06, 0.19)
Month 18	-0.70 (-5.24, 3.83)	10.28 (2.21, 18.35)	-10.99 (-20.21, -1.77), 0.0199	-0.49 (-1.14, 0.16)
No	81	26		
Week 12	0.19 (-1.85, 2.23)	1.49 (-2.01, 5.00)	-1.30 (-5.34, 2.74), 0.5254	-0.23 (-0.67, 0.20)
Week 24	0.77 (-1.35, 2.88)	0.86 (-2.79, 4.51)	-0.10 (-4.29, 4.10), 0.9642	-0.01 (-0.47, 0.44)
Month 9	1.28 (-1.49, 4.06)	6.42 (1.60, 11.25)	-5.14 (-10.69, 0.41), 0.0692	-0.56 (-1.02, -0.10)
Week 48	0.29 (-2.97, 3.55)	4.52 (-1.17, 10.22)	-4.23 (-10.78, 2.31), 0.2036	-0.27 (-0.72, 0.18)
Week 60	1.09 (-1.38, 3.55)	0.05 (-4.28, 4.38)	1.04 (-3.92, 6.00), 0.6802	0.16 (-0.31, 0.63)
Week 72	2.05 (-2.65, 6.76)	7.82 (-0.50, 16.15)	-5.77 (-15.33, 3.78), 0.2340	-0.61 (-1.09, -0.12)
Month 18	2.40 (-1.76, 6.57)	4.97 (-2.37, 12.31)	-2.57 (-11.00, 5.87), 0.5460	-0.26 (-0.72, 0.19)
p-value of Treatment*Cardiac Subpopulation	0.0103			

LS estimates and p-value derived from mixed-effects model for repeated measures (MMRM), controlling for categorical factors (treatment, visit), the subgroup variable, continuous covariate (baseline value), and interaction (treatment by visit, treatment by subgroup).
Standardized effect size (d) = LS mean difference/estimated pooled standard deviation with the small sample bias correction.

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Table 13.2
Cardiac Biomarkers - Troponin T (ng/L): Change from Baseline to Month 18, MMRM Model
Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A) Subgroup Analysis
mITT Population

Subgroup Visit	LS Mean (95% CI) Vutrisiran (HELIOS-A) (N=122)	LS Mean (95% CI) Patisiran (HELIOS-A) (N=42)	LS Mean Difference (Vutrisiran-Patisiran) (95% CI), p-value	Standardized Effect Size (95% CI)
Weight (kg)				
<65	45	15		
Week 12	-1.89 (-4.49, 0.70)	2.20 (-2.33, 6.73)	-4.09 (-9.31, 1.13), 0.1236	-0.42 (-1.01, 0.18)
Week 24	-1.32 (-3.94, 1.31)	1.57 (-3.04, 6.19)	-2.89 (-8.20, 2.42), 0.2845	-0.28 (-0.90, 0.33)
Month 9	-0.80 (-3.98, 2.37)	7.12 (1.55, 12.68)	-7.92 (-14.32, -1.51), 0.0157	-0.46 (-1.05, 0.14)
Week 48	-1.80 (-5.38, 1.79)	5.24 (-1.05, 11.53)	-7.04 (-14.28, 0.21), 0.0568	-0.56 (-1.15, 0.03)
Week 60	-0.99 (-3.92, 1.93)	0.78 (-4.37, 5.93)	-1.77 (-7.70, 4.15), 0.5555	-0.14 (-0.75, 0.48)
Week 72	-0.04 (-4.96, 4.88)	8.50 (-0.23, 17.24)	-8.54 (-18.57, 1.49), 0.0944	-0.48 (-1.09, 0.14)
Month 18	0.31 (-4.06, 4.68)	5.56 (-2.16, 13.28)	-5.25 (-14.13, 3.62), 0.2427	-0.30 (-0.88, 0.29)
≥65	75	24		
Week 12	-0.13 (-2.24, 1.99)	3.86 (0.15, 7.57)	-3.98 (-8.30, 0.33), 0.0700	-0.48 (-0.94, -0.01)
Week 24	0.45 (-1.71, 2.62)	3.23 (-0.55, 7.02)	-2.78 (-7.18, 1.62), 0.2140	-0.28 (-0.75, 0.18)
Month 9	0.96 (-1.84, 3.77)	8.78 (3.85, 13.70)	-7.81 (-13.51, -2.11), 0.0075	-0.82 (-1.31, -0.33)
Week 48	-0.03 (-3.29, 3.23)	6.90 (1.16, 12.64)	-6.93 (-13.56, -0.29), 0.0407	-0.36 (-0.83, 0.11)
Week 60	0.77 (-1.74, 3.28)	2.44 (-2.01, 6.88)	-1.67 (-6.81, 3.47), 0.5229	-0.17 (-0.64, 0.30)
Week 72	1.73 (-2.97, 6.42)	10.16 (1.80, 18.52)	-8.43 (-18.04, 1.17), 0.0848	-0.39 (-0.87, 0.10)
Month 18	2.07 (-2.04, 6.19)	7.22 (-0.06, 14.50)	-5.15 (-13.53, 3.24), 0.2255	-0.41 (-0.90, 0.08)
p-value of Treatment*Weight	0.9737			

LS estimates and p-value derived from mixed-effects model for repeated measures (MMRM), controlling for categorical factors (treatment, visit), the subgroup variable, continuous covariate (baseline value), and interaction (treatment by visit, treatment by subgroup).
Standardized effect size (d) = LS mean difference/estimated pooled standard deviation with the small sample bias correction.

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Table 13.3
Cardiac Biomarkers - Troponin T (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Age (years): <65

Subgroup Visit	Vutrisiran (HELIOS-A) (N=76)	Patisiran (HELIOS-A) (N=31)
Baseline		
n	76	30
Mean (SD)	28.066 (22.525)	34.867 (23.670)
SE	2.584	4.321
Median	18.000	29.500
Min, Max	12.00, 145.00	12.00, 94.00
Week 12		
Actual Value		
n	75	30
Mean (SD)	27.227 (19.940)	34.267 (22.858)
SE	2.302	4.173
Median	19.000	29.500
Min, Max	12.00, 85.00	12.00, 77.00
Change from baseline		
n	75	29
Mean (SD)	-0.720 (8.237)	0.034 (5.402)
SE	0.951	1.003
Median	0.000	0.000
Min, Max	-60.00, 17.00	-10.00, 10.00

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mITT Population

Age (years): <65

Subgroup Visit	Vutrisiran (HELIOS-A) (N=76)	Patisiran (HELIOS-A) (N=31)
Week 24		
Actual Value		
n	75	29
Mean (SD)	27.880 (19.939)	34.414 (24.211)
SE	2.302	4.496
Median	19.000	28.000
Min, Max	12.00, 91.00	12.00, 96.00
Change from baseline		
n	75	28
Mean (SD)	-0.400 (7.378)	-0.464 (4.834)
SE	0.852	0.914
Median	0.000	0.000
Min, Max	-54.00, 11.00	-14.00, 9.00

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Cardiac Biomarkers - Troponin T (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Age (years): <65

Subgroup Visit	Vutrisiran (HELIOS-A) (N=76)	Patisiran (HELIOS-A) (N=31)
Month 9		
Actual Value		
n	73	29
Mean (SD)	28.466 (20.231)	42.207 (41.691)
SE	2.368	7.742
Median	21.000	29.000
Min, Max	12.00, 100.00	12.00, 203.00
Change from baseline		
n	73	28
Mean (SD)	0.658 (8.282)	6.107 (21.526)
SE	0.969	4.068
Median	0.000	0.000
Min, Max	-45.00, 18.00	-12.00, 109.00

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Cardiac Biomarkers - Troponin T (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Age (years): <65

Subgroup Visit	Vutrisiran (HELIOS-A) (N=76)	Patisiran (HELIOS-A) (N=31)
Week 48		
Actual Value		
n	73	29
Mean (SD)	27.205 (19.876)	32.759 (26.239)
SE	2.326	4.872
Median	18.000	23.000
Min, Max	12.00, 86.00	12.00, 107.00
Change from baseline		
n	73	29
Mean (SD)	-0.260 (9.145)	-1.103 (7.903)
SE	1.070	1.468
Median	0.000	0.000
Min, Max	-59.00, 21.00	-17.00, 20.00

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Cardiac Biomarkers - Troponin T (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Age (years): <65

Subgroup Visit	Vutrisiran (HELIOS-A) (N=76)	Patisiran (HELIOS-A) (N=31)
Week 60		
Actual Value		
n	74	27
Mean (SD)	27.878 (20.830)	29.481 (22.280)
SE	2.421	4.288
Median	17.000	23.000
Min, Max	12.00, 89.00	12.00, 93.00
Change from baseline		
n	74	27
Mean (SD)	0.338 (10.051)	-2.889 (6.135)
SE	1.168	1.181
Median	0.000	-1.000
Min, Max	-56.00, 24.00	-21.00, 5.00

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Table 13.3
Cardiac Biomarkers - Troponin T (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Age (years): <65

Subgroup Visit	Vutrisiran (HELIOS-A) (N=76)	Patisiran (HELIOS-A) (N=31)
Week 72		
Actual Value		
n	74	26
Mean (SD)	28.351 (22.714)	31.962 (25.016)
SE	2.640	4.906
Median	18.000	23.500
Min, Max	12.00, 120.00	12.00, 99.00
Change from baseline		
n	74	26
Mean (SD)	0.716 (12.063)	-2.231 (12.401)
SE	1.402	2.432
Median	0.000	0.000
Min, Max	-55.00, 64.00	-34.00, 29.00

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Table 13.3
Cardiac Biomarkers - Troponin T (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Age (years): <65

Subgroup Visit	Vutrisiran (HELIOS-A) (N=76)	Patisiran (HELIOS-A) (N=31)
Month 18		
Actual Value		
n	74	29
Mean (SD)	28.784 (25.888)	31.759 (21.578)
SE	3.009	4.007
Median	17.000	26.000
Min, Max	12.00, 133.00	12.00, 99.00
Change from baseline		
n	74	29
Mean (SD)	1.622 (15.741)	-2.103 (10.728)
SE	1.830	1.992
Median	0.000	0.000
Min, Max	-52.00, 77.00	-25.00, 30.00

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Alnylam Pharmaceuticals Inc.
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Table 13.3
Cardiac Biomarkers - Troponin T (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Age (years): ≥65

Subgroup Visit	Vutrisiran (HELIOS-A) (N=46)	Patisiran (HELIOS-A) (N=11)
Baseline		
n	46	10
Mean (SD)	48.370 (64.183)	68.800 (76.620)
SE	9.463	24.229
Median	35.000	41.500
Min, Max	12.00, 444.00	14.00, 264.00
Week 12		
Actual Value		
n	44	8
Mean (SD)	38.250 (25.738)	88.375 (102.817)
SE	3.880	36.351
Median	33.000	50.500
Min, Max	12.00, 130.00	17.00, 323.00
Change from baseline		
n	44	8
Mean (SD)	-1.227 (7.799)	10.625 (21.771)
SE	1.176	7.697
Median	-1.500	1.500
Min, Max	-28.00, 17.00	-3.00, 59.00

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Table 13.3
Cardiac Biomarkers - Troponin T (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Age (years): ≥65

Subgroup Visit	Vutrisiran (HELIOS-A) (N=46)	Patisiran (HELIOS-A) (N=11)
Week 24		
Actual Value		
n	41	9
Mean (SD)	38.293 (28.766)	86.667 (106.166)
SE	4.492	35.389
Median	31.000	41.000
Min, Max	12.00, 157.00	16.00, 338.00
Change from baseline		
n	41	8
Mean (SD)	-0.317 (10.083)	14.500 (28.405)
SE	1.575	10.043
Median	-2.000	1.500
Min, Max	-28.00, 36.00	-9.00, 74.00

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Table 13.3
Cardiac Biomarkers - Troponin T (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Age (years): ≥65

Subgroup Visit	Vutrisiran (HELIOS-A) (N=46)	Patisiran (HELIOS-A) (N=11)
Month 9		
Actual Value		
n	40	9
Mean (SD)	38.775 (25.055)	57.111 (55.654)
SE	3.962	18.551
Median	34.000	48.000
Min, Max	12.00, 114.00	16.00, 195.00
Change from baseline		
n	40	8
Mean (SD)	-1.125 (9.879)	8.875 (22.351)
SE	1.562	7.902
Median	0.000	3.000
Min, Max	-28.00, 23.00	-12.00, 61.00

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Table 13.3
Cardiac Biomarkers - Troponin T (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Age (years): ≥65

Subgroup Visit	Vutrisiran (HELIOS-A) (N=46)	Patisiran (HELIOS-A) (N=11)
Week 48		
Actual Value		
n	43	10
Mean (SD)	38.326 (24.663)	99.400 (123.551)
SE	3.761	39.070
Median	31.000	47.000
Min, Max	12.00, 108.00	16.00, 369.00
Change from baseline		
n	43	9
Mean (SD)	-1.791 (10.573)	30.333 (56.961)
SE	1.612	18.987
Median	-3.000	1.000
Min, Max	-28.00, 36.00	-12.00, 146.00

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Table 13.3
Cardiac Biomarkers - Troponin T (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Age (years): ≥65

Subgroup Visit	Vutrisiran (HELIOS-A) (N=46)	Patisiran (HELIOS-A) (N=11)
Week 60		
Actual Value		
n	43	9
Mean (SD)	39.209 (27.439)	77.667 (97.527)
SE	4.184	32.509
Median	32.000	40.000
Min, Max	12.00, 145.00	16.00, 321.00
Change from baseline		
n	43	8
Mean (SD)	-0.907 (9.237)	10.750 (27.070)
SE	1.409	9.571
Median	-1.000	-2.000
Min, Max	-23.00, 25.00	-12.00, 57.00

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Table 13.3
Cardiac Biomarkers - Troponin T (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Age (years): ≥65

Subgroup Visit	Vutrisiran (HELIOS-A) (N=46)	Patisiran (HELIOS-A) (N=11)
Week 72		
Actual Value		
n	43	9
Mean (SD)	39.605 (31.137)	95.222 (142.883)
SE	4.748	47.628
Median	29.000	41.000
Min, Max	12.00, 142.00	17.00, 464.00
Change from baseline		
n	43	8
Mean (SD)	1.047 (13.427)	27.625 (71.077)
SE	2.048	25.130
Median	0.000	0.500
Min, Max	-28.00, 46.00	-9.00, 200.00

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Table 13.3
Cardiac Biomarkers - Troponin T (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Age (years): ≥65

Subgroup Visit	Vutrisiran (HELIOS-A) (N=46)	Patisiran (HELIOS-A) (N=11)
Month 18		
Actual Value		
n	39	8
Mean (SD)	39.564 (31.633)	41.250 (22.397)
SE	5.065	7.919
Median	30.000	38.000
Min, Max	12.00, 155.00	17.00, 80.00
Change from baseline		
n	39	7
Mean (SD)	0.487 (13.412)	1.286 (7.521)
SE	2.148	2.843
Median	0.000	-2.000
Min, Max	-28.00, 41.00	-7.00, 16.00

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Table 13.3
Cardiac Biomarkers - Troponin T (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Sex: Male

Subgroup Visit	Vutrisiran (HELIOS-A) (N=79)	Patisiran (HELIOS-A) (N=27)
Baseline		
n	79	25
Mean (SD)	40.709 (51.774)	50.960 (52.027)
SE	5.825	10.405
Median	31.000	42.000
Min, Max	12.00, 444.00	12.00, 264.00
Week 12		
Actual Value		
n	76	24
Mean (SD)	34.803 (22.345)	56.833 (64.131)
SE	2.563	13.091
Median	30.500	36.000
Min, Max	12.00, 93.00	12.00, 323.00
Change from baseline		
n	76	23
Mean (SD)	-0.605 (9.130)	3.522 (14.466)
SE	1.047	3.016
Median	0.000	0.000
Min, Max	-60.00, 17.00	-10.00, 59.00

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Table 13.3
Cardiac Biomarkers - Troponin T (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Sex: Male

Subgroup Visit	Vutrisiran (HELIOS-A) (N=79)	Patisiran (HELIOS-A) (N=27)
Week 24		
Actual Value		
n	75	25
Mean (SD)	34.560 (21.984)	56.760 (67.662)
SE	2.539	13.532
Median	29.000	38.000
Min, Max	12.00, 99.00	12.00, 338.00
Change from baseline		
n	75	23
Mean (SD)	-0.560 (8.664)	4.652 (18.242)
SE	1.000	3.804
Median	0.000	0.000
Min, Max	-54.00, 20.00	-14.00, 74.00

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Table 13.3
Cardiac Biomarkers - Troponin T (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Sex: Male

Subgroup Visit	Vutrisiran (HELIOS-A) (N=79)	Patisiran (HELIOS-A) (N=27)
Month 9		
Actual Value		
n	73	24
Mean (SD)	36.589 (23.470)	49.500 (41.601)
SE	2.747	8.492
Median	32.000	36.500
Min, Max	12.00, 114.00	12.00, 195.00
Change from baseline		
n	73	22
Mean (SD)	0.781 (9.452)	5.136 (15.468)
SE	1.106	3.298
Median	0.000	0.500
Min, Max	-45.00, 23.00	-12.00, 61.00

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Table 13.3
Cardiac Biomarkers - Troponin T (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Sex: Male

Subgroup Visit	Vutrisiran (HELIOS-A) (N=79)	Patisiran (HELIOS-A) (N=27)
Week 48		
Actual Value		
n	74	24
Mean (SD)	36.054 (23.817)	61.417 (86.065)
SE	2.769	17.568
Median	30.000	29.000
Min, Max	12.00, 108.00	12.00, 369.00
Change from baseline		
n	74	23
Mean (SD)	0.054 (10.745)	10.043 (38.837)
SE	1.249	8.098
Median	0.000	0.000
Min, Max	-59.00, 36.00	-17.00, 146.00

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Table 13.3
Cardiac Biomarkers - Troponin T (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Sex: Male

Subgroup Visit	Vutrisiran (HELIOS-A) (N=79)	Patisiran (HELIOS-A) (N=27)
Week 60		
Actual Value		
n	75	23
Mean (SD)	35.347 (23.275)	49.609 (65.387)
SE	2.688	13.634
Median	30.000	30.000
Min, Max	12.00, 94.00	12.00, 321.00
Change from baseline		
n	75	22
Mean (SD)	-0.613 (10.571)	0.273 (18.406)
SE	1.221	3.924
Median	0.000	-2.000
Min, Max	-56.00, 25.00	-21.00, 57.00

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Table 13.3
Cardiac Biomarkers - Troponin T (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Sex: Male

Subgroup Visit	Vutrisiran (HELIOS-A) (N=79)	Patisiran (HELIOS-A) (N=27)
Week 72		
Actual Value		
n	76	22
Mean (SD)	36.329 (27.344)	58.818 (95.267)
SE	3.137	20.311
Median	26.500	32.000
Min, Max	12.00, 142.00	12.00, 464.00
Change from baseline		
n	76	21
Mean (SD)	1.474 (14.221)	8.571 (45.773)
SE	1.631	9.988
Median	0.000	0.000
Min, Max	-55.00, 64.00	-34.00, 200.00

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Table 13.3
Cardiac Biomarkers - Troponin T (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Sex: Male

Subgroup Visit	Vutrisiran (HELIOS-A) (N=79)	Patisiran (HELIOS-A) (N=27)
Month 18		
Actual Value		
n	72	22
Mean (SD)	36.528 (28.923)	35.727 (19.477)
SE	3.409	4.152
Median	26.500	32.500
Min, Max	12.00, 133.00	12.00, 80.00
Change from baseline		
n	72	21
Mean (SD)	1.986 (16.579)	-2.714 (9.665)
SE	1.954	2.109
Median	0.000	0.000
Min, Max	-52.00, 77.00	-23.00, 16.00

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Table 13.3
Cardiac Biomarkers - Troponin T (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Sex: Female

Subgroup Visit	Vutrisiran (HELIOS-A) (N=43)	Patisiran (HELIOS-A) (N=15)
Baseline		
n	43	15
Mean (SD)	26.558 (22.138)	30.667 (25.207)
SE	3.376	6.508
Median	15.000	14.000
Min, Max	12.00, 121.00	12.00, 94.00
Week 12		
Actual Value		
n	43	14
Mean (SD)	25.116 (22.496)	26.500 (19.441)
SE	3.431	5.196
Median	14.000	16.000
Min, Max	12.00, 130.00	12.00, 73.00
Change from baseline		
n	43	14
Mean (SD)	-1.442 (5.717)	0.357 (3.365)
SE	0.872	0.899
Median	0.000	0.000
Min, Max	-28.00, 9.00	-9.00, 5.00

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Table 13.3
Cardiac Biomarkers - Troponin T (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Sex: Female

Subgroup Visit	Vutrisiran (HELIOS-A) (N=43)	Patisiran (HELIOS-A) (N=15)
Week 24		
Actual Value		
n	41	13
Mean (SD)	26.073 (26.324)	27.615 (26.136)
SE	4.111	7.249
Median	14.000	14.000
Min, Max	12.00, 157.00	12.00, 96.00
Change from baseline		
n	41	13
Mean (SD)	-0.024 (7.958)	-0.308 (3.497)
SE	1.243	0.970
Median	0.000	0.000
Min, Max	-28.00, 36.00	-9.00, 6.00

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Table 13.3
Cardiac Biomarkers - Troponin T (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Sex: Female

Subgroup Visit	Vutrisiran (HELIOS-A) (N=43)	Patisiran (HELIOS-A) (N=15)
Month 9		
Actual Value		
n	40	14
Mean (SD)	23.950 (18.194)	39.286 (51.326)
SE	2.877	13.717
Median	13.500	18.500
Min, Max	12.00, 99.00	12.00, 203.00
Change from baseline		
n	40	14
Mean (SD)	-1.350 (7.641)	9.214 (28.941)
SE	1.208	7.735
Median	0.000	0.000
Min, Max	-28.00, 16.00	-2.00, 109.00

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Table 13.3
Cardiac Biomarkers - Troponin T (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Sex: Female

Subgroup Visit	Vutrisiran (HELIOS-A) (N=43)	Patisiran (HELIOS-A) (N=15)
Week 48		
Actual Value		
n	42	15
Mean (SD)	23.000 (16.648)	31.333 (27.986)
SE	2.569	7.226
Median	15.500	18.000
Min, Max	12.00, 94.00	12.00, 104.00
Change from baseline		
n	42	15
Mean (SD)	-2.381 (7.315)	0.667 (6.043)
SE	1.129	1.560
Median	0.000	0.000
Min, Max	-28.00, 9.00	-16.00, 11.00

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Table 13.3
Cardiac Biomarkers - Troponin T (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Sex: Female

Subgroup Visit	Vutrisiran (HELIOS-A) (N=43)	Patisiran (HELIOS-A) (N=15)
Week 60		
Actual Value		
n	42	13
Mean (SD)	26.143 (24.404)	27.231 (23.188)
SE	3.766	6.431
Median	15.500	16.000
Min, Max	12.00, 145.00	12.00, 93.00
Change from baseline		
n	42	13
Mean (SD)	0.762 (8.084)	0.154 (3.436)
SE	1.247	0.953
Median	0.000	0.000
Min, Max	-20.00, 24.00	-7.00, 7.00

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Table 13.3
Cardiac Biomarkers - Troponin T (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Sex: Female

Subgroup Visit	Vutrisiran (HELIOS-A) (N=43)	Patisiran (HELIOS-A) (N=15)
Week 72		
Actual Value		
n	41	13
Mean (SD)	25.366 (23.743)	30.308 (26.603)
SE	3.708	7.378
Median	15.000	17.000
Min, Max	12.00, 141.00	12.00, 98.00
Change from baseline		
n	41	13
Mean (SD)	-0.341 (8.578)	-1.308 (12.828)
SE	1.340	3.558
Median	0.000	0.000
Min, Max	-28.00, 28.00	-28.00, 29.00

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Table 13.3
Cardiac Biomarkers - Troponin T (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Sex: Female

Subgroup Visit	Vutrisiran (HELIOS-A) (N=43)	Patisiran (HELIOS-A) (N=15)
Month 18		
Actual Value		
n	41	15
Mean (SD)	25.439 (26.128)	31.000 (25.281)
SE	4.080	6.528
Median	13.000	19.000
Min, Max	12.00, 155.00	12.00, 99.00
Change from baseline		
n	41	15
Mean (SD)	-0.098 (11.541)	0.333 (10.946)
SE	1.802	2.826
Median	0.000	0.000
Min, Max	-28.00, 41.00	-25.00, 30.00

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Table 13.3
Cardiac Biomarkers - Troponin T (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Race: White

Subgroup Visit	Vutrisiran (HELIOS-A) (N=86)	Patisiran (HELIOS-A) (N=29)
Baseline		
n	86	27
Mean (SD)	33.035 (48.128)	36.407 (23.914)
SE	5.190	4.602
Median	23.500	32.000
Min, Max	12.00, 444.00	12.00, 94.00
Week 12		
Actual Value		
n	83	25
Mean (SD)	27.855 (18.488)	37.560 (25.438)
SE	2.029	5.088
Median	22.000	30.000
Min, Max	12.00, 93.00	12.00, 90.00
Change from baseline		
n	83	24
Mean (SD)	-0.048 (5.787)	1.708 (7.357)
SE	0.635	1.502
Median	0.000	0.000
Min, Max	-28.00, 17.00	-10.00, 26.00

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Table 13.3
Cardiac Biomarkers - Troponin T (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Race: White

Subgroup Visit	Vutrisiran (HELIOS-A) (N=86)	Patisiran (HELIOS-A) (N=29)
Week 24		
Actual Value		
n	82	27
Mean (SD)	28.220 (19.090)	38.815 (25.764)
SE	2.108	4.958
Median	22.500	32.000
Min, Max	12.00, 99.00	12.00, 96.00
Change from baseline		
n	82	25
Mean (SD)	0.317 (5.961)	0.480 (5.067)
SE	0.658	1.013
Median	0.000	0.000
Min, Max	-28.00, 20.00	-9.00, 15.00

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Table 13.3
Cardiac Biomarkers - Troponin T (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Race: White

Subgroup Visit	Vutrisiran (HELIOS-A) (N=86)	Patisiran (HELIOS-A) (N=29)
Month 9		
Actual Value		
n	80	27
Mean (SD)	29.588 (19.716)	46.852 (42.791)
SE	2.204	8.235
Median	25.500	36.000
Min, Max	12.00, 114.00	12.00, 203.00
Change from baseline		
n	80	25
Mean (SD)	1.388 (7.118)	7.680 (22.590)
SE	0.796	4.518
Median	0.000	0.000
Min, Max	-28.00, 18.00	-12.00, 109.00

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Table 13.3
Cardiac Biomarkers - Troponin T (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Race: White

Subgroup Visit	Vutrisiran (HELIOS-A) (N=86)	Patisiran (HELIOS-A) (N=29)
Week 48		
Actual Value		
n	82	27
Mean (SD)	28.476 (19.428)	38.630 (30.374)
SE	2.145	5.845
Median	20.000	28.000
Min, Max	12.00, 108.00	12.00, 107.00
Change from baseline		
n	82	26
Mean (SD)	0.378 (7.251)	1.038 (11.076)
SE	0.801	2.172
Median	0.000	0.000
Min, Max	-28.00, 21.00	-16.00, 41.00

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

Alnylam Pharmaceuticals Inc.
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Table 13.3
Cardiac Biomarkers - Troponin T (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Race: White

Subgroup Visit	Vutrisiran (HELIOS-A) (N=86)	Patisiran (HELIOS-A) (N=29)
Week 60		
Actual Value		
n	82	25
Mean (SD)	29.024 (19.952)	37.280 (30.301)
SE	2.203	6.060
Median	22.500	28.000
Min, Max	12.00, 94.00	12.00, 114.00
Change from baseline		
n	82	24
Mean (SD)	0.707 (7.415)	-0.083 (12.104)
SE	0.819	2.471
Median	0.000	-1.000
Min, Max	-14.00, 24.00	-21.00, 50.00

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

Alnylam Pharmaceuticals Inc.
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Table 13.3
Cardiac Biomarkers - Troponin T (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Race: White

Subgroup Visit	Vutrisiran (HELIOS-A) (N=86)	Patisiran (HELIOS-A) (N=29)
Week 72		
Actual Value		
n	83	24
Mean (SD)	29.193 (23.550)	40.917 (32.740)
SE	2.585	6.683
Median	21.000	27.000
Min, Max	12.00, 142.00	12.00, 116.00
Change from baseline		
n	83	23
Mean (SD)	1.795 (12.488)	0.435 (14.933)
SE	1.371	3.114
Median	0.000	0.000
Min, Max	-28.00, 64.00	-34.00, 36.00

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Alnylam Pharmaceuticals Inc.
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Table 13.3
Cardiac Biomarkers - Troponin T (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Race: White

Subgroup Visit	Vutrisiran (HELIOS-A) (N=86)	Patisiran (HELIOS-A) (N=29)
Month 18		
Actual Value		
n	80	27
Mean (SD)	29.313 (24.884)	36.815 (23.786)
SE	2.782	4.578
Median	19.000	33.000
Min, Max	12.00, 133.00	12.00, 99.00
Change from baseline		
n	80	26
Mean (SD)	2.188 (14.697)	-0.769 (10.970)
SE	1.643	2.151
Median	0.000	0.000
Min, Max	-28.00, 77.00	-25.00, 30.00

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Alnylam Pharmaceuticals Inc.
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Table 13.3
Cardiac Biomarkers - Troponin T (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Race: All Other Races

Subgroup Visit	Vutrisiran (HELIOS-A) (N=36)	Patisiran (HELIOS-A) (N=13)
Baseline		
n	36	13
Mean (SD)	42.139 (32.184)	57.769 (70.028)
SE	5.364	19.422
Median	31.000	42.000
Min, Max	12.00, 145.00	12.00, 264.00
Week 12		
Actual Value		
n	36	13
Mean (SD)	39.250 (29.272)	61.231 (85.304)
SE	4.879	23.659
Median	33.000	33.000
Min, Max	12.00, 130.00	12.00, 323.00
Change from baseline		
n	36	13
Mean (SD)	-2.889 (11.583)	3.462 (17.241)
SE	1.930	4.782
Median	0.000	0.000
Min, Max	-60.00, 15.00	-9.00, 59.00

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Table 13.3
Cardiac Biomarkers - Troponin T (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Race: All Other Races

Subgroup Visit	Vutrisiran (HELIOS-A) (N=36)	Patisiran (HELIOS-A) (N=13)
Week 24		
Actual Value		
n	34	11
Mean (SD)	39.618 (31.503)	66.364 (101.068)
SE	5.403	30.473
Median	31.000	28.000
Min, Max	12.00, 157.00	12.00, 338.00
Change from baseline		
n	34	11
Mean (SD)	-2.029 (12.413)	8.273 (25.675)
SE	2.129	7.741
Median	0.000	0.000
Min, Max	-54.00, 36.00	-14.00, 74.00

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Table 13.3
Cardiac Biomarkers - Troponin T (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Race: All Other Races

Subgroup Visit	Vutrisiran (HELIOS-A) (N=36)	Patisiran (HELIOS-A) (N=13)
Month 9		
Actual Value		
n	33	11
Mean (SD)	38.242 (27.522)	43.000 (52.202)
SE	4.791	15.739
Median	32.000	29.000
Min, Max	12.00, 100.00	12.00, 195.00
Change from baseline		
n	33	11
Mean (SD)	-3.273 (11.614)	4.545 (19.320)
SE	2.022	5.825
Median	0.000	0.000
Min, Max	-45.00, 23.00	-12.00, 61.00

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Alnylam Pharmaceuticals Inc.
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Table 13.3
Cardiac Biomarkers - Troponin T (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Race: All Other Races

Subgroup Visit	Vutrisiran (HELIOS-A) (N=36)	Patisiran (HELIOS-A) (N=13)
Week 48		
Actual Value		
n	34	12
Mean (SD)	38.206 (27.242)	75.083 (118.574)
SE	4.672	34.229
Median	30.500	25.500
Min, Max	12.00, 97.00	12.00, 369.00
Change from baseline		
n	34	12
Mean (SD)	-3.735 (13.612)	17.833 (51.443)
SE	2.334	14.850
Median	-1.000	0.000
Min, Max	-59.00, 36.00	-17.00, 146.00

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Table 13.3
Cardiac Biomarkers - Troponin T (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Race: All Other Races

Subgroup Visit	Vutrisiran (HELIOS-A) (N=36)	Patisiran (HELIOS-A) (N=13)
Week 60		
Actual Value		
n	35	11
Mean (SD)	39.114 (30.700)	51.182 (90.089)
SE	5.189	27.163
Median	30.000	24.000
Min, Max	12.00, 145.00	12.00, 321.00
Change from baseline		
n	35	11
Mean (SD)	-2.057 (13.677)	0.909 (19.695)
SE	2.312	5.938
Median	0.000	-2.000
Min, Max	-56.00, 25.00	-18.00, 57.00

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Table 13.3
Cardiac Biomarkers - Troponin T (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Race: All Other Races

Subgroup Visit	Vutrisiran (HELIOS-A) (N=36)	Patisiran (HELIOS-A) (N=13)
Week 72		
Actual Value		
n	34	11
Mean (SD)	40.529 (31.742)	64.182 (133.037)
SE	5.444	40.112
Median	24.500	25.000
Min, Max	12.00, 141.00	12.00, 464.00
Change from baseline		
n	34	11
Mean (SD)	-1.500 (12.491)	13.909 (61.972)
SE	2.142	18.685
Median	0.000	-2.000
Min, Max	-55.00, 20.00	-17.00, 200.00

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Table 13.3
Cardiac Biomarkers - Troponin T (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Race: All Other Races

Subgroup Visit	Vutrisiran (HELIOS-A) (N=36)	Patisiran (HELIOS-A) (N=13)
Month 18		
Actual Value		
n	33	10
Mean (SD)	40.242 (34.553)	25.700 (12.919)
SE	6.015	4.085
Median	25.000	25.000
Min, Max	12.00, 155.00	12.00, 48.00
Change from baseline		
n	33	10
Mean (SD)	-1.091 (15.452)	-3.200 (7.997)
SE	2.690	2.529
Median	0.000	-1.000
Min, Max	-52.00, 41.00	-18.00, 7.00

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Table 13.3
Cardiac Biomarkers - Troponin T (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Region: North America

Subgroup Visit	Vutrisiran (HELIOS-A) (N=27)	Patisiran (HELIOS-A) (N=8)
Baseline		
n	27	8
Mean (SD)	23.333 (16.717)	67.750 (89.159)
SE	3.217	31.523
Median	17.000	28.000
Min, Max	12.00, 79.00	12.00, 264.00
Week 12		
Actual Value		
n	27	8
Mean (SD)	23.444 (18.128)	75.750 (107.682)
SE	3.489	38.071
Median	16.000	31.500
Min, Max	12.00, 93.00	12.00, 323.00
Change from baseline		
n	27	8
Mean (SD)	0.111 (5.515)	8.000 (20.702)
SE	1.061	7.319
Median	0.000	0.000
Min, Max	-11.00, 17.00	-1.00, 59.00

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Table 13.3
Cardiac Biomarkers - Troponin T (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Region: North America

Subgroup Visit	Vutrisiran (HELIOS-A) (N=27)	Patisiran (HELIOS-A) (N=8)
Week 24		
Actual Value		
n	25	8
Mean (SD)	23.880 (19.178)	82.625 (116.327)
SE	3.836	41.128
Median	17.000	32.500
Min, Max	12.00, 99.00	12.00, 338.00
Change from baseline		
n	25	8
Mean (SD)	-0.080 (6.013)	14.875 (27.456)
SE	1.203	9.707
Median	0.000	1.500
Min, Max	-10.00, 20.00	-2.00, 74.00

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Table 13.3
Cardiac Biomarkers - Troponin T (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Region: North America

Subgroup Visit	Vutrisiran (HELIOS-A) (N=27)	Patisiran (HELIOS-A) (N=8)
Month 9		
Actual Value		
n	23	7
Mean (SD)	22.435 (14.789)	48.286 (66.120)
SE	3.084	24.991
Median	17.000	18.000
Min, Max	12.00, 69.00	12.00, 195.00
Change from baseline		
n	23	7
Mean (SD)	0.000 (5.427)	8.571 (23.172)
SE	1.132	8.758
Median	0.000	0.000
Min, Max	-10.00, 16.00	-2.00, 61.00

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Table 13.3
Cardiac Biomarkers - Troponin T (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Region: North America

Subgroup Visit	Vutrisiran (HELIOS-A) (N=27)	Patisiran (HELIOS-A) (N=8)
Week 48		
Actual Value		
n	25	8
Mean (SD)	23.400 (15.618)	98.375 (142.025)
SE	3.124	50.213
Median	19.000	26.500
Min, Max	12.00, 73.00	12.00, 369.00
Change from baseline		
n	25	8
Mean (SD)	-0.720 (5.892)	30.625 (59.622)
SE	1.178	21.080
Median	0.000	0.500
Min, Max	-11.00, 16.00	-5.00, 146.00

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Table 13.3
Cardiac Biomarkers - Troponin T (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Region: North America

Subgroup Visit	Vutrisiran (HELIOS-A) (N=27)	Patisiran (HELIOS-A) (N=8)
Week 60		
Actual Value		
n	26	7
Mean (SD)	24.192 (17.575)	65.714 (113.318)
SE	3.447	42.830
Median	17.000	18.000
Min, Max	12.00, 86.00	12.00, 321.00
Change from baseline		
n	26	7
Mean (SD)	0.423 (7.234)	7.429 (21.931)
SE	1.419	8.289
Median	0.000	0.000
Min, Max	-11.00, 23.00	-3.00, 57.00

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Table 13.3
Cardiac Biomarkers - Troponin T (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Region: North America

Subgroup Visit	Vutrisiran (HELIOS-A) (N=27)	Patisiran (HELIOS-A) (N=8)
Week 72		
Actual Value		
n	25	5
Mean (SD)	21.840 (13.554)	112.600 (197.083)
SE	2.711	88.138
Median	17.000	19.000
Min, Max	12.00, 59.00	12.00, 464.00
Change from baseline		
n	25	5
Mean (SD)	0.280 (7.334)	40.800 (89.001)
SE	1.467	39.803
Median	0.000	2.000
Min, Max	-13.00, 28.00	0.00, 200.00

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Table 13.3
Cardiac Biomarkers - Troponin T (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Region: North America

Subgroup Visit	Vutrisiran (HELIOS-A) (N=27)	Patisiran (HELIOS-A) (N=8)
Month 18		
Actual Value		
n	24	6
Mean (SD)	20.917 (14.018)	25.333 (15.693)
SE	2.861	6.407
Median	13.500	20.000
Min, Max	12.00, 60.00	12.00, 50.00
Change from baseline		
n	24	6
Mean (SD)	-0.375 (9.903)	1.333 (2.338)
SE	2.021	0.955
Median	0.000	0.500
Min, Max	-15.00, 41.00	0.00, 6.00

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Alnylam Pharmaceuticals Inc.
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Table 13.3
Cardiac Biomarkers - Troponin T (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Region: Western Europe

Subgroup Visit	Vutrisiran (HELIOS-A) (N=42)	Patisiran (HELIOS-A) (N=20)
Baseline		
n	42	19
Mean (SD)	35.810 (66.332)	35.632 (20.246)
SE	10.235	4.645
Median	23.500	32.000
Min, Max	12.00, 444.00	12.00, 69.00
Week 12		
Actual Value		
n	39	17
Mean (SD)	23.949 (15.250)	39.235 (26.321)
SE	2.442	6.384
Median	18.000	34.000
Min, Max	12.00, 81.00	12.00, 90.00
Change from baseline		
n	39	17
Mean (SD)	-1.154 (5.537)	3.294 (7.824)
SE	0.887	1.898
Median	0.000	1.000
Min, Max	-28.00, 8.00	-10.00, 26.00

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Alnylam Pharmaceuticals Inc.
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Table 13.3
Cardiac Biomarkers - Troponin T (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Region: Western Europe

Subgroup Visit	Vutrisiran (HELIOS-A) (N=42)	Patisiran (HELIOS-A) (N=20)
Week 24		
Actual Value		
n	38	16
Mean (SD)	22.368 (11.963)	34.750 (22.180)
SE	1.941	5.545
Median	18.000	29.000
Min, Max	12.00, 62.00	12.00, 79.00
Change from baseline		
n	38	15
Mean (SD)	-0.816 (6.221)	1.000 (5.682)
SE	1.009	1.467
Median	0.000	0.000
Min, Max	-28.00, 10.00	-8.00, 15.00

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Table 13.3
Cardiac Biomarkers - Troponin T (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Region: Western Europe

Subgroup Visit	Vutrisiran (HELIOS-A) (N=42)	Patisiran (HELIOS-A) (N=20)
Month 9		
Actual Value		
n	38	18
Mean (SD)	26.447 (16.503)	39.222 (26.143)
SE	2.677	6.162
Median	23.000	36.500
Min, Max	12.00, 79.00	12.00, 84.00
Change from baseline		
n	38	17
Mean (SD)	1.132 (7.230)	4.353 (9.500)
SE	1.173	2.304
Median	0.500	1.000
Min, Max	-28.00, 13.00	-12.00, 29.00

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Table 13.3
Cardiac Biomarkers - Troponin T (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Region: Western Europe

Subgroup Visit	Vutrisiran (HELIOS-A) (N=42)	Patisiran (HELIOS-A) (N=20)
Week 48		
Actual Value		
n	39	18
Mean (SD)	24.923 (16.435)	36.778 (26.715)
SE	2.632	6.297
Median	19.000	28.500
Min, Max	12.00, 87.00	12.00, 105.00
Change from baseline		
n	39	17
Mean (SD)	-0.179 (7.222)	0.941 (11.908)
SE	1.156	2.888
Median	0.000	0.000
Min, Max	-28.00, 16.00	-16.00, 41.00

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Table 13.3
Cardiac Biomarkers - Troponin T (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Region: Western Europe

Subgroup Visit	Vutrisiran (HELIOS-A) (N=42)	Patisiran (HELIOS-A) (N=20)
Week 60		
Actual Value		
n	39	17
Mean (SD)	25.718 (16.194)	34.941 (28.869)
SE	2.593	7.002
Median	22.000	28.000
Min, Max	12.00, 76.00	12.00, 114.00
Change from baseline		
n	39	16
Mean (SD)	0.154 (5.485)	-0.563 (14.975)
SE	0.878	3.744
Median	0.000	-2.000
Min, Max	-13.00, 21.00	-21.00, 50.00

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Table 13.3
Cardiac Biomarkers - Troponin T (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Region: Western Europe

Subgroup Visit	Vutrisiran (HELIOS-A) (N=42)	Patisiran (HELIOS-A) (N=20)
Week 72		
Actual Value		
n	40	17
Mean (SD)	25.575 (19.111)	40.059 (33.562)
SE	3.022	8.140
Median	19.000	32.000
Min, Max	12.00, 95.00	12.00, 116.00
Change from baseline		
n	40	16
Mean (SD)	0.175 (10.505)	1.875 (15.688)
SE	1.661	3.922
Median	0.000	0.000
Min, Max	-28.00, 42.00	-34.00, 36.00

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Table 13.3
Cardiac Biomarkers - Troponin T (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Region: Western Europe

Subgroup Visit	Vutrisiran (HELIOS-A) (N=42)	Patisiran (HELIOS-A) (N=20)
Month 18		
Actual Value		
n	39	18
Mean (SD)	24.026 (15.076)	36.722 (25.036)
SE	2.414	5.901
Median	18.000	32.500
Min, Max	12.00, 76.00	12.00, 99.00
Change from baseline		
n	39	17
Mean (SD)	-1.103 (7.573)	1.000 (10.712)
SE	1.213	2.598
Median	0.000	0.000
Min, Max	-28.00, 21.00	-18.00, 30.00

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Table 13.3
Cardiac Biomarkers - Troponin T (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Region: Rest of World

Subgroup Visit	Vutrisiran (HELIOS-A) (N=53)	Patisiran (HELIOS-A) (N=14)
Baseline		
n	53	13
Mean (SD)	41.962 (28.207)	39.615 (26.800)
SE	3.875	7.433
Median	42.000	39.000
Min, Max	12.00, 145.00	12.00, 94.00
Week 12		
Actual Value		
n	53	13
Mean (SD)	40.717 (26.099)	35.538 (22.571)
SE	3.585	6.260
Median	38.000	30.000
Min, Max	12.00, 130.00	12.00, 77.00
Change from baseline		
n	53	12
Mean (SD)	-1.245 (10.425)	-2.833 (4.914)
SE	1.432	1.419
Median	0.000	-0.500
Min, Max	-60.00, 17.00	-10.00, 5.00

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

Alnylam Pharmaceuticals Inc.
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Table 13.3
Cardiac Biomarkers - Troponin T (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Region: Rest of World

Subgroup Visit	Vutrisiran (HELIOS-A) (N=53)	Patisiran (HELIOS-A) (N=14)
Week 24		
Actual Value		
n	53	14
Mean (SD)	41.774 (28.099)	40.071 (27.747)
SE	3.860	7.416
Median	41.000	33.000
Min, Max	12.00, 157.00	12.00, 96.00
Change from baseline		
n	53	13
Mean (SD)	-0.189 (10.547)	-2.385 (5.620)
SE	1.449	1.559
Median	0.000	-1.000
Min, Max	-54.00, 36.00	-14.00, 7.00

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

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Table 13.3
Cardiac Biomarkers - Troponin T (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Region: Rest of World

Subgroup Visit	Vutrisiran (HELIOS-A) (N=53)	Patisiran (HELIOS-A) (N=14)
Month 9		
Actual Value		
n	52	13
Mean (SD)	40.538 (26.100)	53.385 (54.431)
SE	3.619	15.097
Median	37.500	30.000
Min, Max	12.00, 114.00	12.00, 203.00
Change from baseline		
n	52	12
Mean (SD)	-0.769 (10.995)	9.000 (31.920)
SE	1.525	9.215
Median	0.000	0.500
Min, Max	-45.00, 23.00	-12.00, 109.00

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

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Table 13.3
Cardiac Biomarkers - Troponin T (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Region: Rest of World

Subgroup Visit	Vutrisiran (HELIOS-A) (N=53)	Patisiran (HELIOS-A) (N=14)
Week 48		
Actual Value		
n	52	13
Mean (SD)	39.942 (25.891)	38.077 (32.454)
SE	3.591	9.001
Median	35.000	25.000
Min, Max	12.00, 108.00	12.00, 107.00
Change from baseline		
n	52	13
Mean (SD)	-1.365 (12.473)	-1.538 (10.485)
SE	1.730	2.908
Median	-0.500	0.000
Min, Max	-59.00, 36.00	-17.00, 20.00

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Alnylam Pharmaceuticals Inc.
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Table 13.3
Cardiac Biomarkers - Troponin T (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Region: Rest of World

Subgroup Visit	Vutrisiran (HELIOS-A) (N=53)	Patisiran (HELIOS-A) (N=14)
Week 60		
Actual Value		
n	52	12
Mean (SD)	40.712 (28.707)	36.750 (28.895)
SE	3.981	8.341
Median	34.500	26.000
Min, Max	12.00, 145.00	12.00, 93.00
Change from baseline		
n	52	12
Mean (SD)	-0.596 (12.930)	-2.917 (6.842)
SE	1.793	1.975
Median	0.000	-0.500
Min, Max	-56.00, 25.00	-18.00, 5.00

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Table 13.3
Cardiac Biomarkers - Troponin T (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Region: Rest of World

Subgroup Visit	Vutrisiran (HELIOS-A) (N=53)	Patisiran (HELIOS-A) (N=14)
Week 72		
Actual Value		
n	52	13
Mean (SD)	42.923 (32.166)	34.154 (25.670)
SE	4.461	7.120
Median	36.000	25.000
Min, Max	12.00, 142.00	12.00, 99.00
Change from baseline		
n	52	13
Mean (SD)	1.615 (15.685)	-5.462 (10.405)
SE	2.175	2.886
Median	0.000	-2.000
Min, Max	-55.00, 64.00	-28.00, 12.00

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Table 13.3
Cardiac Biomarkers - Troponin T (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Region: Rest of World

Subgroup Visit	Vutrisiran (HELIOS-A) (N=53)	Patisiran (HELIOS-A) (N=14)
Month 18		
Actual Value		
n	50	13
Mean (SD)	44.680 (35.947)	33.692 (19.670)
SE	5.084	5.455
Median	30.500	30.000
Min, Max	12.00, 155.00	12.00, 69.00
Change from baseline		
n	50	13
Mean (SD)	3.820 (20.158)	-5.923 (10.626)
SE	2.851	2.947
Median	0.000	-2.000
Min, Max	-52.00, 77.00	-25.00, 7.00

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Alnylam Pharmaceuticals Inc.
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Table 13.3
Cardiac Biomarkers - Troponin T (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Baseline NIS: <50

Subgroup Visit	Vutrisiran (HELIOS-A) (N=78)	Patisiran (HELIOS-A) (N=27)
Baseline		
n	78	26
Mean (SD)	24.167 (17.441)	42.154 (52.972)
SE	1.975	10.389
Median	14.500	26.000
Min, Max	12.00, 82.00	12.00, 264.00
Week 12		
Actual Value		
n	78	25
Mean (SD)	23.910 (17.817)	45.200 (65.242)
SE	2.017	13.048
Median	14.000	24.000
Min, Max	12.00, 93.00	12.00, 323.00
Change from baseline		
n	78	25
Mean (SD)	-0.256 (5.268)	2.640 (13.641)
SE	0.596	2.728
Median	0.000	0.000
Min, Max	-28.00, 17.00	-10.00, 59.00

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Table 13.3
Cardiac Biomarkers - Troponin T (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Baseline NIS: <50

Subgroup Visit	Vutrisiran (HELIOS-A) (N=78)	Patisiran (HELIOS-A) (N=27)
Week 24		
Actual Value		
n	74	27
Mean (SD)	23.135 (17.083)	46.481 (67.221)
SE	1.986	12.937
Median	14.000	28.000
Min, Max	12.00, 99.00	12.00, 338.00
Change from baseline		
n	74	26
Mean (SD)	-0.095 (5.542)	3.846 (17.132)
SE	0.644	3.360
Median	0.000	0.000
Min, Max	-28.00, 20.00	-14.00, 74.00

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Table 13.3
Cardiac Biomarkers - Troponin T (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Baseline NIS: <50

Subgroup Visit	Vutrisiran (HELIOS-A) (N=78)	Patisiran (HELIOS-A) (N=27)
Month 9		
Actual Value		
n	74	25
Mean (SD)	23.459 (16.436)	37.200 (40.007)
SE	1.911	8.001
Median	15.500	21.000
Min, Max	12.00, 79.00	12.00, 195.00
Change from baseline		
n	74	24
Mean (SD)	0.351 (6.420)	3.500 (13.743)
SE	0.746	2.805
Median	0.000	0.000
Min, Max	-28.00, 16.00	-12.00, 61.00

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Table 13.3
Cardiac Biomarkers - Troponin T (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Baseline NIS: <50

Subgroup Visit	Vutrisiran (HELIOS-A) (N=78)	Patisiran (HELIOS-A) (N=27)
Week 48		
Actual Value		
n	76	27
Mean (SD)	23.355 (16.547)	51.222 (82.967)
SE	1.898	15.967
Median	14.500	23.000
Min, Max	12.00, 87.00	12.00, 369.00
Change from baseline		
n	76	26
Mean (SD)	-0.289 (6.312)	8.462 (36.573)
SE	0.724	7.173
Median	0.000	0.000
Min, Max	-28.00, 16.00	-17.00, 146.00

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Table 13.3
Cardiac Biomarkers - Troponin T (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Baseline NIS: <50

Subgroup Visit	Vutrisiran (HELIOS-A) (N=78)	Patisiran (HELIOS-A) (N=27)
Week 60		
Actual Value		
n	76	24
Mean (SD)	24.000 (17.104)	40.583 (64.989)
SE	1.962	13.266
Median	15.500	18.000
Min, Max	12.00, 86.00	12.00, 321.00
Change from baseline		
n	76	23
Mean (SD)	0.355 (5.968)	1.174 (17.606)
SE	0.685	3.671
Median	0.000	0.000
Min, Max	-17.00, 23.00	-21.00, 57.00

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Table 13.3
Cardiac Biomarkers - Troponin T (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Baseline NIS: <50

Subgroup Visit	Vutrisiran (HELIOS-A) (N=78)	Patisiran (HELIOS-A) (N=27)
Week 72		
Actual Value		
n	75	23
Mean (SD)	23.027 (17.007)	50.870 (95.110)
SE	1.964	19.832
Median	15.000	20.000
Min, Max	12.00, 95.00	12.00, 464.00
Change from baseline		
n	75	22
Mean (SD)	0.120 (7.467)	8.409 (44.944)
SE	0.862	9.582
Median	0.000	0.000
Min, Max	-28.00, 28.00	-34.00, 200.00

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Table 13.3
Cardiac Biomarkers - Troponin T (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Baseline NIS: <50

Subgroup Visit	Vutrisiran (HELIOS-A) (N=78)	Patisiran (HELIOS-A) (N=27)
Month 18		
Actual Value		
n	73	25
Mean (SD)	22.000 (15.222)	30.120 (23.080)
SE	1.782	4.616
Median	13.000	24.000
Min, Max	12.00, 73.00	12.00, 99.00
Change from baseline		
n	73	24
Mean (SD)	-0.658 (7.864)	-0.417 (9.934)
SE	0.920	2.028
Median	0.000	0.000
Min, Max	-28.00, 41.00	-18.00, 30.00

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Table 13.3
Cardiac Biomarkers - Troponin T (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Baseline NIS: ≥50

Subgroup Visit	Vutrisiran (HELIOS-A) (N=44)	Patisiran (HELIOS-A) (N=15)
Baseline		
n	44	14
Mean (SD)	56.205 (65.227)	45.571 (23.957)
SE	9.833	6.403
Median	44.000	46.500
Min, Max	14.00, 444.00	14.00, 94.00
Week 12		
Actual Value		
n	41	13
Mean (SD)	45.366 (24.729)	46.538 (21.349)
SE	3.862	5.921
Median	40.000	47.000
Min, Max	13.00, 130.00	17.00, 77.00
Change from baseline		
n	41	12
Mean (SD)	-2.146 (11.631)	1.667 (5.758)
SE	1.816	1.662
Median	-2.000	2.000
Min, Max	-60.00, 17.00	-10.00, 9.00

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Table 13.3
Cardiac Biomarkers - Troponin T (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Baseline NIS: ≥50

Subgroup Visit	Vutrisiran (HELIOS-A) (N=44)	Patisiran (HELIOS-A) (N=15)
Week 24		
Actual Value		
n	42	11
Mean (SD)	46.405 (26.860)	47.545 (28.001)
SE	4.145	8.443
Median	42.000	41.000
Min, Max	14.00, 157.00	17.00, 96.00
Change from baseline		
n	42	10
Mean (SD)	-0.857 (11.932)	0.300 (5.208)
SE	1.841	1.647
Median	-1.000	0.500
Min, Max	-54.00, 36.00	-9.00, 9.00

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Table 13.3
Cardiac Biomarkers - Troponin T (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Baseline NIS: ≥50

Subgroup Visit	Vutrisiran (HELIOS-A) (N=44)	Patisiran (HELIOS-A) (N=15)
Month 9		
Actual Value		
n	39	13
Mean (SD)	48.538 (23.460)	62.154 (51.018)
SE	3.757	14.150
Median	42.000	49.000
Min, Max	18.00, 114.00	16.00, 203.00
Change from baseline		
n	39	12
Mean (SD)	-0.590 (12.350)	13.167 (31.571)
SE	1.978	9.114
Median	0.000	5.000
Min, Max	-45.00, 23.00	-12.00, 109.00

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Table 13.3
Cardiac Biomarkers - Troponin T (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Baseline NIS: ≥50

Subgroup Visit	Vutrisiran (HELIOS-A) (N=44)	Patisiran (HELIOS-A) (N=15)
Week 48		
Actual Value		
n	40	12
Mean (SD)	46.475 (24.176)	46.750 (30.967)
SE	3.823	8.939
Median	43.000	46.000
Min, Max	16.00, 108.00	16.00, 107.00
Change from baseline		
n	40	12
Mean (SD)	-1.850 (14.078)	1.750 (7.875)
SE	2.226	2.273
Median	-2.000	0.500
Min, Max	-59.00, 36.00	-12.00, 20.00

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Table 13.3
Cardiac Biomarkers - Troponin T (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Baseline NIS: ≥50

Subgroup Visit	Vutrisiran (HELIOS-A) (N=44)	Patisiran (HELIOS-A) (N=15)
Week 60		
Actual Value		
n	41	12
Mean (SD)	46.951 (27.757)	43.417 (26.051)
SE	4.335	7.520
Median	39.000	40.500
Min, Max	16.00, 145.00	16.00, 93.00
Change from baseline		
n	41	12
Mean (SD)	-1.000 (14.387)	-1.583 (5.854)
SE	2.247	1.690
Median	-2.000	-1.500
Min, Max	-56.00, 25.00	-12.00, 7.00

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Table 13.3
Cardiac Biomarkers - Troponin T (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Baseline NIS: ≥50

Subgroup Visit	Vutrisiran (HELIOS-A) (N=44)	Patisiran (HELIOS-A) (N=15)
Week 72		
Actual Value		
n	42	12
Mean (SD)	49.381 (31.901)	43.167 (23.832)
SE	4.922	6.880
Median	44.500	42.500
Min, Max	15.00, 142.00	15.00, 99.00
Change from baseline		
n	42	12
Mean (SD)	2.119 (18.455)	-1.833 (11.392)
SE	2.848	3.289
Median	-1.000	0.000
Min, Max	-55.00, 64.00	-28.00, 17.00

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Table 13.3
Cardiac Biomarkers - Troponin T (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Baseline NIS: ≥50

Subgroup Visit	Vutrisiran (HELIOS-A) (N=44)	Patisiran (HELIOS-A) (N=15)
Month 18		
Actual Value		
n	40	12
Mean (SD)	51.675 (35.975)	41.500 (17.265)
SE	5.688	4.984
Median	39.000	42.500
Min, Max	14.00, 155.00	16.00, 69.00
Change from baseline		
n	40	12
Mean (SD)	4.675 (22.514)	-3.500 (10.791)
SE	3.560	3.115
Median	-0.500	-2.000
Min, Max	-52.00, 77.00	-25.00, 10.00

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Table 13.3
Cardiac Biomarkers - Troponin T (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Previous Tetramer Stabilizer Use: Yes

Subgroup Visit	Vutrisiran (HELIOS-A) (N=75)	Patisiran (HELIOS-A) (N=33)
Baseline		
n	75	31
Mean (SD)	31.920 (24.593)	36.355 (23.558)
SE	2.840	4.231
Median	25.000	30.000
Min, Max	12.00, 145.00	12.00, 94.00
Week 12		
Actual Value		
n	73	30
Mean (SD)	30.753 (23.014)	37.200 (24.859)
SE	2.694	4.539
Median	23.000	31.500
Min, Max	12.00, 130.00	12.00, 90.00
Change from baseline		
n	73	29
Mean (SD)	-0.932 (9.329)	1.379 (6.847)
SE	1.092	1.272
Median	0.000	0.000
Min, Max	-60.00, 17.00	-10.00, 26.00

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Table 13.3
Cardiac Biomarkers - Troponin T (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Previous Tetramer Stabilizer Use: Yes

Subgroup Visit	Vutrisiran (HELIOS-A) (N=75)	Patisiran (HELIOS-A) (N=33)
Week 24		
Actual Value		
n	73	30
Mean (SD)	31.863 (25.027)	36.733 (25.124)
SE	2.929	4.587
Median	25.000	30.000
Min, Max	12.00, 157.00	12.00, 96.00
Change from baseline		
n	73	28
Mean (SD)	-0.164 (9.605)	0.000 (5.650)
SE	1.124	1.068
Median	0.000	0.000
Min, Max	-54.00, 36.00	-14.00, 15.00

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Table 13.3
Cardiac Biomarkers - Troponin T (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Previous Tetramer Stabilizer Use: Yes

Subgroup Visit	Vutrisiran (HELIOS-A) (N=75)	Patisiran (HELIOS-A) (N=33)
Month 9		
Actual Value		
n	74	32
Mean (SD)	31.541 (21.309)	44.281 (39.959)
SE	2.477	7.064
Median	26.000	32.500
Min, Max	12.00, 100.00	12.00, 203.00
Change from baseline		
n	74	30
Mean (SD)	-0.216 (9.515)	6.367 (20.909)
SE	1.106	3.818
Median	0.000	1.000
Min, Max	-45.00, 18.00	-12.00, 109.00

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Table 13.3
Cardiac Biomarkers - Troponin T (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Previous Tetramer Stabilizer Use: Yes

Subgroup Visit	Vutrisiran (HELIOS-A) (N=75)	Patisiran (HELIOS-A) (N=33)
Week 48		
Actual Value		
n	73	31
Mean (SD)	30.753 (21.347)	37.226 (28.906)
SE	2.498	5.192
Median	24.000	28.000
Min, Max	12.00, 94.00	12.00, 107.00
Change from baseline		
n	73	30
Mean (SD)	-0.932 (10.441)	0.800 (10.370)
SE	1.222	1.893
Median	0.000	0.000
Min, Max	-59.00, 21.00	-17.00, 41.00

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Table 13.3
Cardiac Biomarkers - Troponin T (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Previous Tetramer Stabilizer Use: Yes

Subgroup Visit	Vutrisiran (HELIOS-A) (N=75)	Patisiran (HELIOS-A) (N=33)
Week 60		
Actual Value		
n	72	30
Mean (SD)	32.694 (25.569)	35.300 (28.090)
SE	3.013	5.128
Median	24.500	28.000
Min, Max	12.00, 145.00	12.00, 114.00
Change from baseline		
n	72	29
Mean (SD)	0.486 (10.670)	-0.966 (11.413)
SE	1.258	2.119
Median	0.000	-1.000
Min, Max	-56.00, 24.00	-21.00, 50.00

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Table 13.3
Cardiac Biomarkers - Troponin T (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Previous Tetramer Stabilizer Use: Yes

Subgroup Visit	Vutrisiran (HELIOS-A) (N=75)	Patisiran (HELIOS-A) (N=33)
Week 72		
Actual Value		
n	72	29
Mean (SD)	31.931 (26.703)	37.448 (30.700)
SE	3.147	5.701
Median	22.000	25.000
Min, Max	12.00, 141.00	12.00, 116.00
Change from baseline		
n	72	28
Mean (SD)	0.556 (13.774)	-0.429 (13.694)
SE	1.623	2.588
Median	0.000	0.000
Min, Max	-55.00, 64.00	-34.00, 36.00

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

Alnylam Pharmaceuticals Inc.
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Table 13.3
Cardiac Biomarkers - Troponin T (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Previous Tetramer Stabilizer Use: Yes

Subgroup Visit	Vutrisiran (HELIOS-A) (N=75)	Patisiran (HELIOS-A) (N=33)
Month 18		
Actual Value		
n	69	31
Mean (SD)	32.261 (30.490)	35.161 (22.878)
SE	3.671	4.109
Median	19.000	32.000
Min, Max	12.00, 155.00	12.00, 99.00
Change from baseline		
n	69	30
Mean (SD)	1.696 (16.636)	-1.267 (10.651)
SE	2.003	1.945
Median	0.000	0.000
Min, Max	-52.00, 77.00	-25.00, 30.00

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

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Table 13.3
Cardiac Biomarkers - Troponin T (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Previous Tetramer Stabilizer Use: No

Subgroup Visit	Vutrisiran (HELIOS-A) (N=47)	Patisiran (HELIOS-A) (N=9)
Baseline		
n	47	9
Mean (SD)	41.787 (63.874)	67.444 (82.408)
SE	9.317	27.469
Median	29.000	39.000
Min, Max	12.00, 444.00	12.00, 264.00
Week 12		
Actual Value		
n	46	8
Mean (SD)	32.174 (22.650)	77.375 (106.589)
SE	3.340	37.685
Median	25.000	31.500
Min, Max	12.00, 89.00	12.00, 323.00
Change from baseline		
n	46	8
Mean (SD)	-0.870 (5.532)	5.750 (22.057)
SE	0.816	7.798
Median	0.000	0.000
Min, Max	-16.00, 15.00	-9.00, 59.00

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Table 13.3
Cardiac Biomarkers - Troponin T (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Previous Tetramer Stabilizer Use: No

Subgroup Visit	Vutrisiran (HELIOS-A) (N=47)	Patisiran (HELIOS-A) (N=9)
Week 24		
Actual Value		
n	43	8
Mean (SD)	31.047 (21.973)	84.500 (115.028)
SE	3.351	40.669
Median	22.000	34.000
Min, Max	12.00, 91.00	12.00, 338.00
Change from baseline		
n	43	8
Mean (SD)	-0.721 (5.865)	12.875 (28.732)
SE	0.894	10.158
Median	0.000	0.500
Min, Max	-10.00, 20.00	-9.00, 74.00

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

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Table 13.3
Cardiac Biomarkers - Troponin T (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Previous Tetramer Stabilizer Use: No

Subgroup Visit	Vutrisiran (HELIOS-A) (N=47)	Patisiran (HELIOS-A) (N=9)
Month 9		
Actual Value		
n	39	6
Mean (SD)	33.205 (24.857)	53.500 (70.775)
SE	3.980	28.894
Median	27.000	26.000
Min, Max	12.00, 114.00	12.00, 195.00
Change from baseline		
n	39	6
Mean (SD)	0.487 (7.619)	8.500 (25.898)
SE	1.220	10.573
Median	0.000	-0.500
Min, Max	-17.00, 23.00	-8.00, 61.00

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Table 13.3
Cardiac Biomarkers - Troponin T (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Previous Tetramer Stabilizer Use: No

Subgroup Visit	Vutrisiran (HELIOS-A) (N=47)	Patisiran (HELIOS-A) (N=9)
Week 48		
Actual Value		
n	43	8
Mean (SD)	32.302 (24.134)	98.750 (141.698)
SE	3.680	50.098
Median	24.000	24.500
Min, Max	12.00, 108.00	12.00, 369.00
Change from baseline		
n	43	8
Mean (SD)	-0.651 (8.352)	27.125 (62.102)
SE	1.274	21.956
Median	0.000	0.500
Min, Max	-15.00, 36.00	-16.00, 146.00

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Table 13.3
Cardiac Biomarkers - Troponin T (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Previous Tetramer Stabilizer Use: No

Subgroup Visit	Vutrisiran (HELIOS-A) (N=47)	Patisiran (HELIOS-A) (N=9)
Week 60		
Actual Value		
n	45	6
Mean (SD)	31.000 (21.474)	72.667 (122.317)
SE	3.201	49.936
Median	25.000	21.000
Min, Max	12.00, 94.00	12.00, 321.00
Change from baseline		
n	45	6
Mean (SD)	-1.089 (8.045)	6.000 (25.954)
SE	1.199	10.596
Median	0.000	-0.500
Min, Max	-20.00, 25.00	-18.00, 57.00

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Table 13.3
Cardiac Biomarkers - Troponin T (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Previous Tetramer Stabilizer Use: No

Subgroup Visit	Vutrisiran (HELIOS-A) (N=47)	Patisiran (HELIOS-A) (N=9)
Week 72		
Actual Value		
n	45	6
Mean (SD)	33.378 (26.604)	100.333 (178.705)
SE	3.966	72.956
Median	25.000	27.500
Min, Max	12.00, 142.00	12.00, 464.00
Change from baseline		
n	45	6
Mean (SD)	1.289 (10.350)	29.167 (83.989)
SE	1.543	34.288
Median	0.000	-0.500
Min, Max	-15.00, 46.00	-17.00, 200.00

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Table 13.3
Cardiac Biomarkers - Troponin T (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Previous Tetramer Stabilizer Use: No

Subgroup Visit	Vutrisiran (HELIOS-A) (N=47)	Patisiran (HELIOS-A) (N=9)
Month 18		
Actual Value		
n	44	6
Mean (SD)	32.886 (24.913)	26.833 (14.580)
SE	3.756	5.952
Median	25.000	24.500
Min, Max	12.00, 111.00	12.00, 50.00
Change from baseline		
n	44	6
Mean (SD)	0.500 (11.910)	-2.333 (8.140)
SE	1.795	3.323
Median	0.000	0.000
Min, Max	-20.00, 41.00	-18.00, 6.00

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Table 13.3
Cardiac Biomarkers - Troponin T (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Genotype: V30M

Subgroup Visit	Vutrisiran (HELIOS-A) (N=54)	Patisiran (HELIOS-A) (N=20)
Baseline		
n	54	20
Mean (SD)	26.370 (19.927)	31.400 (18.838)
SE	2.712	4.212
Median	17.000	29.000
Min, Max	12.00, 121.00	12.00, 69.00
Week 12		
Actual Value		
n	52	19
Mean (SD)	24.750 (20.152)	31.842 (21.027)
SE	2.795	4.824
Median	17.500	25.000
Min, Max	12.00, 130.00	12.00, 76.00
Change from baseline		
n	52	19
Mean (SD)	-1.077 (5.967)	0.474 (5.232)
SE	0.827	1.200
Median	0.000	0.000
Min, Max	-28.00, 11.00	-10.00, 10.00

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Table 13.3
Cardiac Biomarkers - Troponin T (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Genotype: V30M

Subgroup Visit	Vutrisiran (HELIOS-A) (N=54)	Patisiran (HELIOS-A) (N=20)
Week 24		
Actual Value		
n	53	18
Mean (SD)	26.113 (23.606)	28.500 (17.534)
SE	3.243	4.133
Median	17.000	25.500
Min, Max	12.00, 157.00	12.00, 66.00
Change from baseline		
n	53	18
Mean (SD)	0.075 (7.470)	-1.000 (4.765)
SE	1.026	1.123
Median	0.000	0.000
Min, Max	-28.00, 36.00	-9.00, 9.00

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Table 13.3
Cardiac Biomarkers - Troponin T (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Genotype: V30M

Subgroup Visit	Vutrisiran (HELIOS-A) (N=54)	Patisiran (HELIOS-A) (N=20)
Month 9		
Actual Value		
n	50	19
Mean (SD)	25.320 (17.151)	34.263 (24.837)
SE	2.425	5.698
Median	18.000	21.000
Min, Max	12.00, 99.00	12.00, 84.00
Change from baseline		
n	50	19
Mean (SD)	-1.120 (7.156)	3.263 (8.730)
SE	1.012	2.003
Median	0.000	0.000
Min, Max	-28.00, 13.00	-12.00, 29.00

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Table 13.3
Cardiac Biomarkers - Troponin T (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Genotype: V30M

Subgroup Visit	Vutrisiran (HELIOS-A) (N=54)	Patisiran (HELIOS-A) (N=20)
Week 48		
Actual Value		
n	51	20
Mean (SD)	24.333 (16.782)	29.050 (18.975)
SE	2.350	4.243
Median	19.000	21.500
Min, Max	12.00, 94.00	12.00, 80.00
Change from baseline		
n	51	20
Mean (SD)	-1.706 (7.027)	-2.350 (6.426)
SE	0.984	1.437
Median	0.000	0.000
Min, Max	-28.00, 12.00	-16.00, 11.00

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Table 13.3
Cardiac Biomarkers - Troponin T (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Genotype: V30M

Subgroup Visit	Vutrisiran (HELIOS-A) (N=54)	Patisiran (HELIOS-A) (N=20)
Week 60		
Actual Value		
n	52	18
Mean (SD)	26.404 (22.848)	25.056 (13.357)
SE	3.169	3.148
Median	17.000	19.500
Min, Max	12.00, 145.00	12.00, 47.00
Change from baseline		
n	52	18
Mean (SD)	0.231 (6.170)	-3.833 (6.437)
SE	0.856	1.517
Median	0.000	-2.000
Min, Max	-13.00, 24.00	-21.00, 7.00

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Table 13.3
Cardiac Biomarkers - Troponin T (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Genotype: V30M

Subgroup Visit	Vutrisiran (HELIOS-A) (N=54)	Patisiran (HELIOS-A) (N=20)
Week 72		
Actual Value		
n	53	18
Mean (SD)	25.585 (22.795)	30.000 (21.633)
SE	3.131	5.099
Median	17.000	21.000
Min, Max	12.00, 141.00	12.00, 98.00
Change from baseline		
n	53	18
Mean (SD)	-0.453 (9.029)	-1.778 (12.754)
SE	1.240	3.006
Median	0.000	0.000
Min, Max	-28.00, 42.00	-34.00, 29.00

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Table 13.3
Cardiac Biomarkers - Troponin T (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Genotype: V30M

Subgroup Visit	Vutrisiran (HELIOS-A) (N=54)	Patisiran (HELIOS-A) (N=20)
Month 18		
Actual Value		
n	51	20
Mean (SD)	25.235 (24.183)	31.250 (21.440)
SE	3.386	4.794
Median	16.000	28.500
Min, Max	12.00, 155.00	12.00, 99.00
Change from baseline		
n	51	20
Mean (SD)	0.020 (8.496)	-0.150 (9.190)
SE	1.190	2.055
Median	0.000	0.000
Min, Max	-28.00, 34.00	-18.00, 30.00

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Table 13.3
Cardiac Biomarkers - Troponin T (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Genotype: non-V30M

Subgroup Visit	Vutrisiran (HELIOS-A) (N=68)	Patisiran (HELIOS-A) (N=22)
Baseline		
n	68	20
Mean (SD)	43.147 (55.413)	55.300 (58.609)
SE	6.720	13.105
Median	31.500	39.500
Min, Max	12.00, 444.00	12.00, 264.00
Week 12		
Actual Value		
n	67	19
Mean (SD)	36.388 (23.549)	59.474 (71.659)
SE	2.877	16.440
Median	33.000	34.000
Min, Max	12.00, 93.00	12.00, 323.00
Change from baseline		
n	67	18
Mean (SD)	-0.776 (9.395)	4.278 (15.740)
SE	1.148	3.710
Median	0.000	0.000
Min, Max	-60.00, 17.00	-10.00, 59.00

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Table 13.3
Cardiac Biomarkers - Troponin T (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Genotype: non-V30M

Subgroup Visit	Vutrisiran (HELIOS-A) (N=68)	Patisiran (HELIOS-A) (N=22)
Week 24		
Actual Value		
n	63	20
Mean (SD)	36.143 (23.252)	63.250 (75.627)
SE	2.929	16.911
Median	31.000	40.500
Min, Max	12.00, 99.00	12.00, 338.00
Change from baseline		
n	63	18
Mean (SD)	-0.746 (9.135)	6.722 (19.926)
SE	1.151	4.697
Median	0.000	0.500
Min, Max	-54.00, 20.00	-14.00, 74.00

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Table 13.3
Cardiac Biomarkers - Troponin T (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Genotype: non-V30M

Subgroup Visit	Vutrisiran (HELIOS-A) (N=68)	Patisiran (HELIOS-A) (N=22)
Month 9		
Actual Value		
n	63	19
Mean (SD)	37.508 (24.804)	57.211 (57.187)
SE	3.125	13.120
Median	34.000	34.000
Min, Max	12.00, 114.00	12.00, 203.00
Change from baseline		
n	63	17
Mean (SD)	0.937 (10.000)	10.588 (29.793)
SE	1.260	7.226
Median	0.000	0.000
Min, Max	-45.00, 23.00	-12.00, 109.00

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Table 13.3
Cardiac Biomarkers - Troponin T (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Genotype: non-V30M

Subgroup Visit	Vutrisiran (HELIOS-A) (N=68)	Patisiran (HELIOS-A) (N=22)
Week 48		
Actual Value		
n	65	19
Mean (SD)	36.815 (24.623)	71.737 (95.769)
SE	3.054	21.971
Median	31.000	29.000
Min, Max	12.00, 108.00	12.00, 369.00
Change from baseline		
n	65	18
Mean (SD)	-0.138 (11.348)	16.000 (42.370)
SE	1.408	9.987
Median	0.000	0.500
Min, Max	-59.00, 36.00	-17.00, 146.00

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Table 13.3
Cardiac Biomarkers - Troponin T (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Genotype: non-V30M

Subgroup Visit	Vutrisiran (HELIOS-A) (N=68)	Patisiran (HELIOS-A) (N=22)
Week 60		
Actual Value		
n	65	18
Mean (SD)	36.554 (24.105)	58.000 (73.513)
SE	2.990	17.327
Median	30.000	30.000
Min, Max	12.00, 94.00	12.00, 321.00
Change from baseline		
n	65	17
Mean (SD)	-0.400 (11.890)	4.529 (19.268)
SE	1.475	4.673
Median	0.000	0.000
Min, Max	-56.00, 25.00	-18.00, 57.00

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Table 13.3
Cardiac Biomarkers - Troponin T (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Genotype: non-V30M

Subgroup Visit	Vutrisiran (HELIOS-A) (N=68)	Patisiran (HELIOS-A) (N=22)
Week 72		
Actual Value		
n	64	17
Mean (SD)	38.203 (28.226)	67.529 (107.662)
SE	3.528	26.112
Median	29.000	27.000
Min, Max	12.00, 142.00	12.00, 464.00
Change from baseline		
n	64	16
Mean (SD)	1.906 (14.799)	12.188 (51.797)
SE	1.850	12.949
Median	0.000	0.000
Min, Max	-55.00, 64.00	-28.00, 200.00

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Table 13.3
Cardiac Biomarkers - Troponin T (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Genotype: non-V30M

Subgroup Visit	Vutrisiran (HELIOS-A) (N=68)	Patisiran (HELIOS-A) (N=22)
Month 18		
Actual Value		
n	62	17
Mean (SD)	38.484 (30.234)	36.824 (22.492)
SE	3.840	5.455
Median	28.500	30.000
Min, Max	12.00, 133.00	12.00, 80.00
Change from baseline		
n	62	16
Mean (SD)	2.226 (18.647)	-3.063 (11.393)
SE	2.368	2.848
Median	0.000	0.000
Min, Max	-52.00, 77.00	-25.00, 16.00

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Table 13.3
Cardiac Biomarkers - Troponin T (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

FAP Stage: I

Subgroup Visit	Vutrisiran (HELIOS-A) (N=84)	Patisiran (HELIOS-A) (N=31)
Baseline		
n	84	30
Mean (SD)	24.595 (16.728)	32.400 (21.203)
SE	1.825	3.871
Median	16.000	28.500
Min, Max	12.00, 76.00	12.00, 94.00
Week 12		
Actual Value		
n	84	27
Mean (SD)	24.369 (16.734)	30.444 (21.806)
SE	1.826	4.197
Median	17.000	24.000
Min, Max	12.00, 80.00	12.00, 90.00
Change from baseline		
n	84	27
Mean (SD)	-0.226 (5.012)	0.370 (6.896)
SE	0.547	1.327
Median	0.000	0.000
Min, Max	-28.00, 17.00	-10.00, 26.00

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Table 13.3
Cardiac Biomarkers - Troponin T (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

FAP Stage: I

Subgroup Visit	Vutrisiran (HELIOS-A) (N=84)	Patisiran (HELIOS-A) (N=31)
Week 24		
Actual Value		
n	82	30
Mean (SD)	24.476 (16.597)	32.700 (22.321)
SE	1.833	4.075
Median	17.000	27.000
Min, Max	12.00, 78.00	12.00, 96.00
Change from baseline		
n	82	29
Mean (SD)	-0.341 (5.226)	-0.552 (5.654)
SE	0.577	1.050
Median	0.000	0.000
Min, Max	-28.00, 10.00	-14.00, 15.00

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Table 13.3
Cardiac Biomarkers - Troponin T (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

FAP Stage: I

Subgroup Visit	Vutrisiran (HELIOS-A) (N=84)	Patisiran (HELIOS-A) (N=31)
Month 9		
Actual Value		
n	80	29
Mean (SD)	24.675 (16.031)	38.069 (39.269)
SE	1.792	7.292
Median	17.000	24.000
Min, Max	12.00, 76.00	12.00, 203.00
Change from baseline		
n	80	28
Mean (SD)	0.525 (6.685)	5.429 (21.911)
SE	0.747	4.141
Median	0.000	0.000
Min, Max	-28.00, 16.00	-12.00, 109.00

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

Alnylam Pharmaceuticals Inc.
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Table 13.3
Cardiac Biomarkers - Troponin T (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

FAP Stage: I

Subgroup Visit	Vutrisiran (HELIOS-A) (N=84)	Patisiran (HELIOS-A) (N=31)
Week 48		
Actual Value		
n	81	30
Mean (SD)	23.951 (15.498)	32.300 (26.125)
SE	1.722	4.770
Median	17.000	23.000
Min, Max	12.00, 74.00	12.00, 105.00
Change from baseline		
n	81	29
Mean (SD)	-0.284 (6.384)	-1.241 (10.699)
SE	0.709	1.987
Median	0.000	0.000
Min, Max	-28.00, 16.00	-17.00, 41.00

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

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Table 13.3
Cardiac Biomarkers - Troponin T (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

FAP Stage: I

Subgroup Visit	Vutrisiran (HELIOS-A) (N=84)	Patisiran (HELIOS-A) (N=31)
Week 60		
Actual Value		
n	82	28
Mean (SD)	24.073 (15.192)	31.214 (26.924)
SE	1.678	5.088
Median	16.500	20.500
Min, Max	12.00, 72.00	12.00, 114.00
Change from baseline		
n	82	27
Mean (SD)	-0.049 (6.340)	-1.815 (12.064)
SE	0.700	2.322
Median	0.000	-1.000
Min, Max	-23.00, 23.00	-21.00, 50.00

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

Alnylam Pharmaceuticals Inc.
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Table 13.3
Cardiac Biomarkers - Troponin T (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

FAP Stage: I

Subgroup Visit	Vutrisiran (HELIOS-A) (N=84)	Patisiran (HELIOS-A) (N=31)
Week 72		
Actual Value		
n	82	27
Mean (SD)	23.354 (15.622)	33.370 (29.171)
SE	1.725	5.614
Median	17.000	22.000
Min, Max	12.00, 77.00	12.00, 116.00
Change from baseline		
n	82	26
Mean (SD)	-0.768 (7.530)	-2.308 (13.838)
SE	0.832	2.714
Median	0.000	0.000
Min, Max	-28.00, 28.00	-34.00, 36.00

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

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Table 13.3
Cardiac Biomarkers - Troponin T (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

FAP Stage: I

Subgroup Visit	Vutrisiran (HELIOS-A) (N=84)	Patisiran (HELIOS-A) (N=31)
Month 18		
Actual Value		
n	79	30
Mean (SD)	23.468 (17.312)	32.667 (22.793)
SE	1.948	4.161
Median	15.000	25.500
Min, Max	12.00, 81.00	12.00, 99.00
Change from baseline		
n	79	29
Mean (SD)	-0.025 (7.884)	-0.793 (10.424)
SE	0.887	1.936
Median	0.000	0.000
Min, Max	-28.00, 41.00	-25.00, 30.00

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

Alnylam Pharmaceuticals Inc.
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Table 13.3
Cardiac Biomarkers - Troponin T (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

FAP Stage: II&III

Subgroup Visit	Vutrisiran (HELIOS-A) (N=38)	Patisiran (HELIOS-A) (N=11)
Baseline		
n	38	10
Mean (SD)	60.316 (69.484)	76.200 (74.754)
SE	11.272	23.639
Median	44.500	51.500
Min, Max	12.00, 444.00	14.00, 264.00
Week 12		
Actual Value		
n	35	11
Mean (SD)	47.943 (26.737)	83.000 (85.844)
SE	4.519	25.883
Median	43.000	59.000
Min, Max	12.00, 130.00	17.00, 323.00
Change from baseline		
n	35	10
Mean (SD)	-2.543 (12.634)	7.600 (18.916)
SE	2.135	5.982
Median	-2.000	4.500
Min, Max	-60.00, 17.00	-10.00, 59.00

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Alnylam Pharmaceuticals Inc.
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Table 13.3
Cardiac Biomarkers - Troponin T (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

FAP Stage: II&III

Subgroup Visit	Vutrisiran (HELIOS-A) (N=38)	Patisiran (HELIOS-A) (N=11)
Week 24		
Actual Value		
n	34	8
Mean (SD)	48.647 (29.664)	99.625 (108.628)
SE	5.087	38.406
Median	44.500	66.500
Min, Max	12.00, 157.00	17.00, 338.00
Change from baseline		
n	34	7
Mean (SD)	-0.441 (13.351)	17.000 (28.983)
SE	2.290	10.954
Median	-1.500	3.000
Min, Max	-54.00, 36.00	-4.00, 74.00

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Table 13.3
Cardiac Biomarkers - Troponin T (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

FAP Stage: II&III

Subgroup Visit	Vutrisiran (HELIOS-A) (N=38)	Patisiran (HELIOS-A) (N=11)
Month 9		
Actual Value		
n	33	9
Mean (SD)	50.152 (25.759)	70.444 (55.448)
SE	4.484	18.483
Median	42.000	49.000
Min, Max	12.00, 114.00	20.00, 195.00
Change from baseline		
n	33	8
Mean (SD)	-1.182 (12.783)	11.250 (20.289)
SE	2.225	7.173
Median	0.000	5.500
Min, Max	-45.00, 23.00	-1.00, 61.00

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Table 13.3
Cardiac Biomarkers - Troponin T (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

FAP Stage: II&III

Subgroup Visit	Vutrisiran (HELIOS-A) (N=38)	Patisiran (HELIOS-A) (N=11)
Week 48		
Actual Value		
n	35	9
Mean (SD)	48.400 (26.297)	108.333 (127.412)
SE	4.445	42.471
Median	43.000	50.000
Min, Max	12.00, 108.00	18.00, 369.00
Change from baseline		
n	35	9
Mean (SD)	-2.086 (14.793)	30.778 (55.052)
SE	2.501	18.351
Median	-2.000	3.000
Min, Max	-59.00, 36.00	-2.00, 146.00

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Table 13.3
Cardiac Biomarkers - Troponin T (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

FAP Stage: II&III

Subgroup Visit	Vutrisiran (HELIOS-A) (N=38)	Patisiran (HELIOS-A) (N=11)
Week 60		
Actual Value		
n	35	8
Mean (SD)	50.714 (30.041)	77.625 (101.204)
SE	5.078	35.781
Median	40.000	44.000
Min, Max	12.00, 145.00	16.00, 321.00
Change from baseline		
n	35	8
Mean (SD)	-0.286 (15.091)	7.125 (20.629)
SE	2.551	7.293
Median	-2.000	-0.500
Min, Max	-56.00, 25.00	-7.00, 57.00

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Table 13.3
Cardiac Biomarkers - Troponin T (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

FAP Stage: II&III

Subgroup Visit	Vutrisiran (HELIOS-A) (N=38)	Patisiran (HELIOS-A) (N=11)
Week 72		
Actual Value		
n	35	8
Mean (SD)	53.886 (33.951)	98.375 (150.011)
SE	5.739	53.037
Median	50.000	48.500
Min, Max	12.00, 142.00	15.00, 464.00
Change from baseline		
n	35	8
Mean (SD)	4.600 (19.477)	27.875 (70.001)
SE	3.292	24.749
Median	0.000	2.000
Min, Max	-55.00, 64.00	-8.00, 200.00

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Table 13.3
Cardiac Biomarkers - Troponin T (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

FAP Stage: II&III

Subgroup Visit	Vutrisiran (HELIOS-A) (N=38)	Patisiran (HELIOS-A) (N=11)
Month 18		
Actual Value		
n	34	7
Mean (SD)	53.500 (36.969)	38.714 (17.509)
SE	6.340	6.618
Median	42.000	42.000
Min, Max	12.00, 155.00	16.00, 64.00
Change from baseline		
n	34	7
Mean (SD)	4.147 (24.429)	-4.143 (9.317)
SE	4.190	3.522
Median	-0.500	-2.000
Min, Max	-52.00, 77.00	-23.00, 5.00

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Table 13.3
Cardiac Biomarkers - Troponin T (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Cardiac Subpopulation: Yes

Subgroup Visit	Vutrisiran (HELIOS-A) (N=40)	Patisiran (HELIOS-A) (N=14)
Baseline		
n	40	13
Mean (SD)	54.400 (68.016)	61.769 (65.536)
SE	10.754	18.177
Median	42.000	42.000
Min, Max	12.00, 444.00	18.00, 264.00
Week 12		
Actual Value		
n	38	12
Mean (SD)	42.921 (21.839)	68.583 (84.026)
SE	3.543	24.256
Median	38.500	44.000
Min, Max	12.00, 89.00	17.00, 323.00
Change from baseline		
n	38	11
Mean (SD)	-1.684 (11.759)	6.455 (19.816)
SE	1.908	5.975
Median	-0.500	0.000
Min, Max	-60.00, 17.00	-10.00, 59.00

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Table 13.3
Cardiac Biomarkers - Troponin T (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Cardiac Subpopulation: Yes

Subgroup Visit	Vutrisiran (HELIOS-A) (N=40)	Patisiran (HELIOS-A) (N=14)
Week 24		
Actual Value		
n	38	13
Mean (SD)	42.658 (22.173)	69.538 (85.395)
SE	3.597	23.684
Median	39.000	36.000
Min, Max	12.00, 91.00	16.00, 338.00
Change from baseline		
n	38	12
Mean (SD)	-1.526 (11.123)	6.083 (22.460)
SE	1.804	6.484
Median	0.000	-0.500
Min, Max	-54.00, 20.00	-14.00, 74.00

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Table 13.3
Cardiac Biomarkers - Troponin T (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Cardiac Subpopulation: Yes

Subgroup Visit	Vutrisiran (HELIOS-A) (N=40)	Patisiran (HELIOS-A) (N=14)
Month 9		
Actual Value		
n	37	13
Mean (SD)	46.027 (24.431)	58.846 (52.808)
SE	4.016	14.646
Median	40.000	36.000
Min, Max	12.00, 114.00	16.00, 203.00
Change from baseline		
n	37	12
Mean (SD)	2.108 (11.990)	9.667 (32.131)
SE	1.971	9.276
Median	2.000	2.500
Min, Max	-45.00, 23.00	-12.00, 109.00

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Table 13.3
Cardiac Biomarkers - Troponin T (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Cardiac Subpopulation: Yes

Subgroup Visit	Vutrisiran (HELIOS-A) (N=40)	Patisiran (HELIOS-A) (N=14)
Week 48		
Actual Value		
n	37	13
Mean (SD)	44.811 (24.509)	72.923 (95.630)
SE	4.029	26.523
Median	43.000	29.000
Min, Max	12.00, 108.00	16.00, 369.00
Change from baseline		
n	37	13
Mean (SD)	1.054 (14.573)	11.154 (31.688)
SE	2.396	8.789
Median	0.000	0.000
Min, Max	-59.00, 36.00	-17.00, 105.00

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Table 13.3
Cardiac Biomarkers - Troponin T (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Cardiac Subpopulation: Yes

Subgroup Visit	Vutrisiran (HELIOS-A) (N=40)	Patisiran (HELIOS-A) (N=14)
Week 60		
Actual Value		
n	37	13
Mean (SD)	43.027 (23.487)	68.000 (82.820)
SE	3.861	22.970
Median	35.000	32.000
Min, Max	12.00, 94.00	16.00, 321.00
Change from baseline		
n	37	13
Mean (SD)	-1.216 (14.709)	6.231 (21.588)
SE	2.418	5.987
Median	-2.000	-2.000
Min, Max	-56.00, 25.00	-12.00, 57.00

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Table 13.3
Cardiac Biomarkers - Troponin T (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Cardiac Subpopulation: Yes

Subgroup Visit	Vutrisiran (HELIOS-A) (N=40)	Patisiran (HELIOS-A) (N=14)
Week 72		
Actual Value		
n	38	13
Mean (SD)	46.368 (29.588)	76.538 (119.978)
SE	4.800	33.276
Median	40.000	32.000
Min, Max	12.00, 142.00	15.00, 464.00
Change from baseline		
n	38	13
Mean (SD)	2.789 (19.359)	14.769 (57.575)
SE	3.140	15.968
Median	0.500	0.000
Min, Max	-55.00, 64.00	-28.00, 200.00

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Table 13.3
Cardiac Biomarkers - Troponin T (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Cardiac Subpopulation: Yes

Subgroup Visit	Vutrisiran (HELIOS-A) (N=40)	Patisiran (HELIOS-A) (N=14)
Month 18		
Actual Value		
n	36	12
Mean (SD)	48.528 (32.364)	40.833 (21.148)
SE	5.394	6.105
Median	35.500	33.500
Min, Max	12.00, 133.00	16.00, 80.00
Change from baseline		
n	36	12
Mean (SD)	4.833 (22.537)	-4.083 (12.064)
SE	3.756	3.483
Median	3.000	-2.000
Min, Max	-52.00, 77.00	-25.00, 16.00

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Table 13.3
Cardiac Biomarkers - Troponin T (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Cardiac Subpopulation: No

Subgroup Visit	Vutrisiran (HELIOS-A) (N=82)	Patisiran (HELIOS-A) (N=28)
Baseline		
n	82	27
Mean (SD)	26.610 (20.506)	34.481 (27.488)
SE	2.265	5.290
Median	18.000	30.000
Min, Max	12.00, 121.00	12.00, 134.00
Week 12		
Actual Value		
n	81	26
Mean (SD)	25.852 (21.241)	35.077 (28.817)
SE	2.360	5.651
Median	18.000	27.000
Min, Max	12.00, 130.00	12.00, 133.00
Change from baseline		
n	81	26
Mean (SD)	-0.543 (5.584)	0.577 (5.077)
SE	0.620	0.996
Median	0.000	0.000
Min, Max	-28.00, 17.00	-10.00, 10.00

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Table 13.3
Cardiac Biomarkers - Troponin T (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Cardiac Subpopulation: No

Subgroup Visit	Vutrisiran (HELIOS-A) (N=82)	Patisiran (HELIOS-A) (N=28)
Week 24		
Actual Value		
n	78	25
Mean (SD)	26.154 (22.861)	34.960 (33.913)
SE	2.588	6.783
Median	17.000	26.000
Min, Max	12.00, 157.00	12.00, 173.00
Change from baseline		
n	78	24
Mean (SD)	0.192 (6.686)	1.250 (9.176)
SE	0.757	1.873
Median	0.000	0.000
Min, Max	-28.00, 36.00	-9.00, 39.00

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Table 13.3
Cardiac Biomarkers - Troponin T (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Cardiac Subpopulation: No

Subgroup Visit	Vutrisiran (HELIOS-A) (N=82)	Patisiran (HELIOS-A) (N=28)
Month 9		
Actual Value		
n	76	25
Mean (SD)	25.342 (18.097)	38.920 (39.851)
SE	2.076	7.970
Median	17.000	21.000
Min, Max	12.00, 99.00	12.00, 195.00
Change from baseline		
n	76	24
Mean (SD)	-0.987 (6.746)	5.250 (14.053)
SE	0.774	2.869
Median	0.000	0.000
Min, Max	-28.00, 16.00	-8.00, 61.00

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Table 13.3
Cardiac Biomarkers - Troponin T (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Cardiac Subpopulation: No

Subgroup Visit	Vutrisiran (HELIOS-A) (N=82)	Patisiran (HELIOS-A) (N=28)
Week 48		
Actual Value		
n	79	26
Mean (SD)	25.013 (18.199)	38.308 (52.748)
SE	2.048	10.345
Median	19.000	21.500
Min, Max	12.00, 94.00	12.00, 280.00
Change from baseline		
n	79	25
Mean (SD)	-1.709 (6.142)	3.840 (30.266)
SE	0.691	6.053
Median	0.000	0.000
Min, Max	-28.00, 9.00	-16.00, 146.00

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Table 13.3
Cardiac Biomarkers - Troponin T (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Cardiac Subpopulation: No

Subgroup Visit	Vutrisiran (HELIOS-A) (N=82)	Patisiran (HELIOS-A) (N=28)
Week 60		
Actual Value		
n	80	23
Mean (SD)	26.963 (22.614)	26.565 (19.190)
SE	2.528	4.001
Median	17.500	18.000
Min, Max	12.00, 145.00	12.00, 93.00
Change from baseline		
n	80	22
Mean (SD)	0.388 (6.312)	-3.318 (6.614)
SE	0.706	1.410
Median	0.000	-0.500
Min, Max	-17.00, 24.00	-21.00, 7.00

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Table 13.3
Cardiac Biomarkers - Troponin T (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Cardiac Subpopulation: No

Subgroup Visit	Vutrisiran (HELIOS-A) (N=82)	Patisiran (HELIOS-A) (N=28)
Week 72		
Actual Value		
n	79	22
Mean (SD)	25.810 (22.243)	31.500 (27.959)
SE	2.503	5.961
Median	17.000	19.500
Min, Max	12.00, 141.00	12.00, 116.00
Change from baseline		
n	79	21
Mean (SD)	-0.101 (7.265)	-1.381 (11.809)
SE	0.817	2.577
Median	0.000	0.000
Min, Max	-28.00, 28.00	-34.00, 29.00

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Table 13.3
Cardiac Biomarkers - Troponin T (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Cardiac Subpopulation: No

Subgroup Visit	Vutrisiran (HELIOS-A) (N=82)	Patisiran (HELIOS-A) (N=28)
Month 18		
Actual Value		
n	77	25
Mean (SD)	25.013 (22.852)	30.440 (21.716)
SE	2.604	4.343
Median	15.000	24.000
Min, Max	12.00, 155.00	12.00, 99.00
Change from baseline		
n	77	24
Mean (SD)	-0.455 (9.243)	-0.125 (9.090)
SE	1.053	1.856
Median	0.000	0.000
Min, Max	-28.00, 41.00	-18.00, 30.00

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Alnylam Pharmaceuticals Inc.
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Table 13.3
Cardiac Biomarkers - Troponin T (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Weight (kg): <65

Subgroup Visit	Vutrisiran (HELIOS-A) (N=46)	Patisiran (HELIOS-A) (N=15)
Baseline		
n	46	15
Mean (SD)	48.457 (66.474)	37.133 (25.040)
SE	9.801	6.465
Median	31.000	37.000
Min, Max	12.00, 444.00	12.00, 94.00
Week 12		
Actual Value		
n	44	14
Mean (SD)	37.500 (26.002)	33.786 (22.161)
SE	3.920	5.923
Median	32.500	31.500
Min, Max	12.00, 130.00	12.00, 76.00
Change from baseline		
n	44	14
Mean (SD)	-2.227 (10.127)	0.714 (5.327)
SE	1.527	1.424
Median	0.000	0.000
Min, Max	-60.00, 9.00	-9.00, 10.00

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Alnylam Pharmaceuticals Inc.
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Table 13.3
Cardiac Biomarkers - Troponin T (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Weight (kg): <65

Subgroup Visit	Vutrisiran (HELIOS-A) (N=46)	Patisiran (HELIOS-A) (N=15)
Week 24		
Actual Value		
n	44	13
Mean (SD)	38.386 (28.603)	34.462 (26.056)
SE	4.312	7.227
Median	31.000	30.000
Min, Max	12.00, 157.00	12.00, 96.00
Change from baseline		
n	44	13
Mean (SD)	-0.977 (10.730)	-0.923 (4.462)
SE	1.618	1.238
Median	0.000	0.000
Min, Max	-54.00, 36.00	-9.00, 6.00

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Alnylam Pharmaceuticals Inc.
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Table 13.3
Cardiac Biomarkers - Troponin T (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Weight (kg): <65

Subgroup Visit	Vutrisiran (HELIOS-A) (N=46)	Patisiran (HELIOS-A) (N=15)
Month 9		
Actual Value		
n	44	14
Mean (SD)	38.773 (25.401)	46.786 (51.090)
SE	3.829	13.654
Median	32.500	34.500
Min, Max	12.00, 114.00	12.00, 203.00
Change from baseline		
n	44	14
Mean (SD)	-0.068 (11.240)	9.786 (29.258)
SE	1.695	7.820
Median	0.500	0.000
Min, Max	-45.00, 18.00	-8.00, 109.00

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Alnylam Pharmaceuticals Inc.
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Table 13.3
Cardiac Biomarkers - Troponin T (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Weight (kg): <65

Subgroup Visit	Vutrisiran (HELIOS-A) (N=46)	Patisiran (HELIOS-A) (N=15)
Week 48		
Actual Value		
n	43	15
Mean (SD)	37.465 (24.320)	35.000 (27.350)
SE	3.709	7.062
Median	30.000	26.000
Min, Max	12.00, 108.00	12.00, 104.00
Change from baseline		
n	43	15
Mean (SD)	-1.419 (12.142)	-2.133 (8.202)
SE	1.852	2.118
Median	0.000	0.000
Min, Max	-59.00, 21.00	-16.00, 11.00

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Alnylam Pharmaceuticals Inc.
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Table 13.3
Cardiac Biomarkers - Troponin T (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Weight (kg): <65

Subgroup Visit	Vutrisiran (HELIOS-A) (N=46)	Patisiran (HELIOS-A) (N=15)
Week 60		
Actual Value		
n	43	13
Mean (SD)	39.372 (28.461)	30.769 (22.870)
SE	4.340	6.343
Median	34.000	28.000
Min, Max	12.00, 145.00	12.00, 93.00
Change from baseline		
n	43	13
Mean (SD)	0.070 (13.348)	-3.769 (7.485)
SE	2.036	2.076
Median	0.000	-1.000
Min, Max	-56.00, 24.00	-21.00, 5.00

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Alnylam Pharmaceuticals Inc.
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Table 13.3
Cardiac Biomarkers - Troponin T (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Weight (kg): <65

Subgroup Visit	Vutrisiran (HELIOS-A) (N=46)	Patisiran (HELIOS-A) (N=15)
Week 72		
Actual Value		
n	44	13
Mean (SD)	40.386 (33.055)	35.462 (25.363)
SE	4.983	7.034
Median	26.000	32.000
Min, Max	12.00, 142.00	12.00, 98.00
Change from baseline		
n	44	13
Mean (SD)	1.545 (16.584)	-3.615 (16.681)
SE	2.500	4.626
Median	0.000	0.000
Min, Max	-55.00, 64.00	-34.00, 29.00

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Alnylam Pharmaceuticals Inc.
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Table 13.3
Cardiac Biomarkers - Troponin T (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Weight (kg): <65

Subgroup Visit	Vutrisiran (HELIOS-A) (N=46)	Patisiran (HELIOS-A) (N=15)
Month 18		
Actual Value		
n	42	15
Mean (SD)	41.048 (34.597)	34.867 (24.410)
SE	5.338	6.303
Median	27.500	33.000
Min, Max	12.00, 155.00	12.00, 99.00
Change from baseline		
n	42	15
Mean (SD)	2.857 (18.203)	-2.267 (12.629)
SE	2.809	3.261
Median	0.000	0.000
Min, Max	-52.00, 77.00	-25.00, 30.00

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Alnylam Pharmaceuticals Inc.
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Table 13.3
Cardiac Biomarkers - Troponin T (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Weight (kg): ≥65

Subgroup Visit	Vutrisiran (HELIOS-A) (N=76)	Patisiran (HELIOS-A) (N=27)
Baseline		
n	76	25
Mean (SD)	28.013 (18.046)	47.080 (53.234)
SE	2.070	10.647
Median	23.000	32.000
Min, Max	12.00, 82.00	12.00, 264.00
Week 12		
Actual Value		
n	75	24
Mean (SD)	27.667 (19.974)	52.583 (65.320)
SE	2.306	13.333
Median	19.000	31.500
Min, Max	12.00, 93.00	12.00, 323.00
Change from baseline		
n	75	23
Mean (SD)	-0.133 (6.486)	3.304 (14.160)
SE	0.749	2.952
Median	0.000	0.000
Min, Max	-28.00, 17.00	-10.00, 59.00

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Alnylam Pharmaceuticals Inc.
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Table 13.3
Cardiac Biomarkers - Troponin T (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Weight (kg): ≥65

Subgroup Visit	Vutrisiran (HELIOS-A) (N=76)	Patisiran (HELIOS-A) (N=27)
Week 24		
Actual Value		
n	72	25
Mean (SD)	27.389 (19.468)	53.200 (68.976)
SE	2.294	13.795
Median	19.000	32.000
Min, Max	12.00, 99.00	12.00, 338.00
Change from baseline		
n	72	23
Mean (SD)	0.000 (6.627)	5.000 (18.018)
SE	0.781	3.757
Median	0.000	0.000
Min, Max	-28.00, 20.00	-14.00, 74.00

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Table 13.3
Cardiac Biomarkers - Troponin T (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Weight (kg): ≥65

Subgroup Visit	Vutrisiran (HELIOS-A) (N=76)	Patisiran (HELIOS-A) (N=27)
Month 9		
Actual Value		
n	69	24
Mean (SD)	27.870 (19.463)	45.125 (42.230)
SE	2.343	8.620
Median	19.000	29.500
Min, Max	12.00, 84.00	12.00, 195.00
Change from baseline		
n	69	22
Mean (SD)	0.087 (7.064)	4.773 (14.979)
SE	0.850	3.194
Median	0.000	0.500
Min, Max	-28.00, 23.00	-12.00, 61.00

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Table 13.3
Cardiac Biomarkers - Troponin T (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Weight (kg): ≥65

Subgroup Visit	Vutrisiran (HELIOS-A) (N=76)	Patisiran (HELIOS-A) (N=27)
Week 48		
Actual Value		
n	73	24
Mean (SD)	27.712 (20.386)	59.125 (86.938)
SE	2.386	17.746
Median	20.000	27.000
Min, Max	12.00, 97.00	12.00, 369.00
Change from baseline		
n	73	23
Mean (SD)	-0.479 (7.962)	11.870 (38.002)
SE	0.932	7.924
Median	0.000	0.000
Min, Max	-28.00, 36.00	-17.00, 146.00

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Alnylam Pharmaceuticals Inc.
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Table 13.3
Cardiac Biomarkers - Troponin T (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Weight (kg): ≥65

Subgroup Visit	Vutrisiran (HELIOS-A) (N=76)	Patisiran (HELIOS-A) (N=27)
Week 60		
Actual Value		
n	74	23
Mean (SD)	27.784 (19.971)	47.609 (66.071)
SE	2.322	13.777
Median	20.000	23.000
Min, Max	12.00, 86.00	12.00, 321.00
Change from baseline		
n	74	22
Mean (SD)	-0.230 (6.939)	2.591 (17.256)
SE	0.807	3.679
Median	0.000	-1.000
Min, Max	-17.00, 25.00	-12.00, 57.00

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Alnylam Pharmaceuticals Inc.
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Table 13.3
Cardiac Biomarkers - Troponin T (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Weight (kg): ≥65

Subgroup Visit	Vutrisiran (HELIOS-A) (N=76)	Patisiran (HELIOS-A) (N=27)
Week 72		
Actual Value		
n	73	22
Mean (SD)	27.726 (20.562)	55.773 (96.272)
SE	2.407	20.525
Median	19.000	22.500
Min, Max	12.00, 95.00	12.00, 464.00
Change from baseline		
n	73	21
Mean (SD)	0.411 (9.381)	10.000 (44.628)
SE	1.098	9.739
Median	0.000	0.000
Min, Max	-28.00, 42.00	-17.00, 200.00

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Alnylam Pharmaceuticals Inc.
ALN-TTRSC02-002

Table 13.3
Cardiac Biomarkers - Troponin T (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Weight (kg): ≥65

Subgroup Visit	Vutrisiran (HELIOS-A) (N=76)	Patisiran (HELIOS-A) (N=27)
Month 18		
Actual Value		
n	71	22
Mean (SD)	27.451 (22.666)	33.091 (20.405)
SE	2.690	4.350
Median	18.000	25.500
Min, Max	12.00, 117.00	12.00, 80.00
Change from baseline		
n	71	21
Mean (SD)	0.268 (12.646)	-0.857 (8.296)
SE	1.501	1.810
Median	0.000	0.000
Min, Max	-28.00, 73.00	-23.00, 16.00

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Troponin I

Alnylam Pharmaceuticals Inc.
ALN-TTRSC02-002

Table 14.2
Cardiac Biomarkers - Troponin I (ng/L): Change from Baseline to Month 18, MMRM Model
Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A) Subgroup Analysis
mITT Population

Subgroup Visit	LS Mean (95% CI) Vutrisiran (HELIOS-A) (N=122)	LS Mean (95% CI) Patisiran (HELIOS-A) (N=42)	LS Mean Difference (Vutrisiran-Patisiran) (95% CI), p-value	Standardized Effect Size (95% CI)
Age (years)				
<65	76	31		
Week 12	3.99 (-6.11, 14.08)	11.43 (-5.17, 28.04)	-7.45 (-26.92, 12.02), 0.4528	-0.13 (-0.55, 0.28)
Week 24	3.94 (-6.16, 14.03)	-4.73 (-21.62, 12.15)	8.67 (-11.04, 28.38), 0.3878	0.57 (0.13, 1.01)
Month 9	3.57 (-6.58, 13.72)	17.01 (0.24, 33.78)	-13.44 (-33.08, 6.20), 0.1794	-0.20 (-0.63, 0.23)
Week 48	1.90 (-8.25, 12.04)	-8.47 (-25.39, 8.44)	10.37 (-9.39, 30.13), 0.3030	0.18 (-0.25, 0.61)
Week 60	3.96 (-6.15, 14.07)	5.53 (-11.43, 22.50)	-1.57 (-21.36, 18.21), 0.8758	-0.09 (-0.53, 0.34)
Week 72	3.47 (-6.66, 13.60)	-0.46 (-17.53, 16.62)	3.93 (-15.96, 23.81), 0.6982	0.07 (-0.37, 0.51)
Month 18	1.62 (-8.51, 11.74)	22.98 (6.13, 39.84)	-21.36 (-41.06, -1.67), 0.0335	-0.80 (-1.24, -0.35)
≥65	44	10		
Week 12	-1.92 (-13.49, 9.65)	49.01 (26.16, 71.85)	-50.93 (-76.57, -25.28), 0.0001	-1.13 (-1.87, -0.39)
Week 24	-1.97 (-13.54, 9.61)	32.84 (9.96, 55.73)	-34.81 (-60.50, -9.12), 0.0081	-0.81 (-1.57, -0.04)
Month 9	-2.33 (-13.96, 9.30)	54.59 (31.82, 77.35)	-56.92 (-82.52, -31.32), 1.638E-05	-1.32 (-2.08, -0.56)
Week 48	-4.01 (-15.64, 7.62)	29.10 (6.39, 51.82)	-33.11 (-58.67, -7.55), 0.0113	-0.64 (-1.34, 0.05)
Week 60	-1.94 (-13.52, 9.63)	43.11 (20.20, 66.02)	-45.05 (-70.76, -19.35), 0.0006	-1.18 (-1.95, -0.40)
Week 72	-2.43 (-14.05, 9.18)	37.12 (14.16, 60.07)	-39.55 (-65.32, -13.79), 0.0027	-0.64 (-1.36, 0.09)
Month 18	-4.28 (-15.91, 7.35)	60.56 (37.61, 83.51)	-64.84 (-90.61, -39.08), 1.171E-06	-0.69 (-1.45, 0.07)
p-value of Treatment*Age	0.0005			

LS estimates and p-value derived from mixed-effects model for repeated measures (MMRM), controlling for categorical factors (treatment, visit), the subgroup variable, continuous covariate (baseline value), and interaction (treatment by visit, treatment by subgroup).
Standardized effect size (d) = LS mean difference/estimated pooled standard deviation with the small sample bias correction.

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Alnylam Pharmaceuticals Inc.
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Table 14.2
Cardiac Biomarkers - Troponin I (ng/L): Change from Baseline to Month 18, MMRM Model
Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A) Subgroup Analysis
mITT Population

Subgroup Visit	LS Mean (95% CI) Vutrisiran (HELIOS-A) (N=122)	LS Mean (95% CI) Patisiran (HELIOS-A) (N=42)	LS Mean Difference (Vutrisiran-Patisiran) (95% CI), p-value	Standardized Effect Size (95% CI)
Sex				
Male	77	26		
Week 12	2.70 (-7.49, 12.90)	25.48 (7.94, 43.01)	-22.77 (-43.06, -2.49), 0.0279	-0.89 (-1.36, -0.43)
Week 24	2.65 (-7.54, 12.85)	9.63 (-8.15, 27.41)	-6.98 (-27.48, 13.53), 0.5041	-0.35 (-0.81, 0.11)
Month 9	2.28 (-7.95, 12.52)	31.43 (13.80, 49.05)	-29.14 (-49.53, -8.76), 0.0052	-1.42 (-1.92, -0.92)
Week 48	0.61 (-9.62, 10.84)	6.38 (-11.44, 24.21)	-5.77 (-26.32, 14.79), 0.5816	-0.16 (-0.61, 0.30)
Week 60	2.66 (-7.52, 12.84)	20.02 (2.15, 37.89)	-17.36 (-37.93, 3.21), 0.0979	-0.59 (-1.07, -0.11)
Week 72	2.18 (-8.03, 12.40)	14.20 (-3.84, 32.23)	-12.01 (-32.75, 8.72), 0.2554	-0.23 (-0.70, 0.23)
Month 18	0.34 (-9.87, 10.56)	37.30 (19.49, 55.12)	-36.96 (-57.50, -16.42), 0.0004	-0.54 (-1.02, -0.06)
Female	43	15		
Week 12	0.58 (-11.33, 12.49)	11.05 (-9.35, 31.46)	-10.47 (-34.22, 13.27), 0.3864	-0.13 (-0.71, 0.45)
Week 24	0.53 (-11.38, 12.44)	-4.80 (-25.35, 15.75)	5.33 (-18.54, 29.20), 0.6610	0.15 (-0.48, 0.79)
Month 9	0.16 (-11.82, 12.15)	17.00 (-3.50, 37.50)	-16.84 (-40.70, 7.02), 0.1661	-0.17 (-0.78, 0.43)
Week 48	-1.51 (-13.50, 10.48)	-8.04 (-28.46, 12.37)	6.53 (-17.26, 30.33), 0.5895	0.08 (-0.51, 0.66)
Week 60	0.54 (-11.41, 12.49)	5.59 (-14.97, 26.16)	-5.06 (-28.96, 18.85), 0.6777	-0.25 (-0.87, 0.36)
Week 72	0.06 (-11.91, 12.03)	-0.23 (-20.78, 20.33)	0.29 (-23.61, 24.19), 0.9810	0.00 (-0.63, 0.64)
Month 18	-1.78 (-13.76, 10.20)	22.88 (2.39, 43.36)	-24.66 (-48.50, -0.81), 0.0427	-0.69 (-1.31, -0.08)
p-value of Treatment*Sex	0.2935			

LS estimates and p-value derived from mixed-effects model for repeated measures (MMRM), controlling for categorical factors (treatment, visit), the subgroup variable, continuous covariate (baseline value), and interaction (treatment by visit, treatment by subgroup).
Standardized effect size (d) = LS mean difference/estimated pooled standard deviation with the small sample bias correction.

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Alnylam Pharmaceuticals Inc.
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Table 14.2
Cardiac Biomarkers - Troponin I (ng/L): Change from Baseline to Month 18, MMRM Model
Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A) Subgroup Analysis
mITT Population

Subgroup Visit	LS Mean (95% CI) Vutrisiran (HELIOS-A) (N=122)	LS Mean (95% CI) Patisiran (HELIOS-A) (N=42)	LS Mean Difference (Vutrisiran-Patisiran) (95% CI), p-value	Standardized Effect Size (95% CI)
Race				
White	84	28		
Week 12	4.67 (-5.34, 14.69)	15.92 (-1.38, 33.22)	-11.25 (-31.32, 8.82), 0.2714	-0.20 (-0.63, 0.23)
Week 24	4.62 (-5.40, 14.64)	0.21 (-17.20, 17.62)	4.41 (-15.75, 24.58), 0.6674	0.17 (-0.27, 0.62)
Month 9	4.24 (-5.83, 14.30)	22.00 (4.68, 39.33)	-17.77 (-37.88, 2.35), 0.0833	-0.26 (-0.69, 0.18)
Week 48	2.56 (-7.50, 12.61)	-3.10 (-20.44, 14.24)	5.66 (-14.47, 25.78), 0.5811	0.09 (-0.34, 0.52)
Week 60	4.59 (-5.41, 14.60)	10.50 (-7.01, 28.01)	-5.91 (-26.15, 14.34), 0.5668	-0.21 (-0.66, 0.24)
Week 72	4.12 (-5.91, 14.16)	4.74 (-12.77, 22.25)	-0.62 (-20.87, 19.64), 0.9523	-0.01 (-0.46, 0.44)
Month 18	2.29 (-7.75, 12.34)	27.79 (10.37, 45.21)	-25.49 (-45.68, -5.31), 0.0134	-0.70 (-1.16, -0.25)
All Other Races	36	13		
Week 12	-4.37 (-16.87, 8.13)	29.12 (7.91, 50.33)	-33.49 (-58.11, -8.87), 0.0078	-0.94 (-1.59, -0.29)
Week 24	-4.42 (-16.92, 8.09)	13.41 (-8.17, 34.98)	-17.83 (-42.76, 7.11), 0.1606	-0.64 (-1.33, 0.04)
Month 9	-4.81 (-17.38, 7.77)	35.20 (13.79, 56.61)	-40.01 (-64.84, -15.18), 0.0017	-1.65 (-2.41, -0.90)
Week 48	-6.49 (-19.06, 6.09)	10.10 (-11.52, 31.72)	-16.58 (-41.60, 8.43), 0.1931	-0.40 (-1.05, 0.25)
Week 60	-4.45 (-17.00, 8.10)	23.70 (2.13, 45.27)	-28.15 (-53.10, -3.19), 0.0272	-1.21 (-1.92, -0.49)
Week 72	-4.92 (-17.48, 7.65)	17.94 (-3.90, 39.78)	-22.86 (-48.05, 2.34), 0.0753	-0.34 (-1.01, 0.33)
Month 18	-6.75 (-19.31, 5.81)	40.98 (19.43, 62.53)	-47.73 (-72.68, -22.79), 0.0002	-0.52 (-1.20, 0.16)
p-value of Treatment*Race	0.0688			

LS estimates and p-value derived from mixed-effects model for repeated measures (MMRM), controlling for categorical factors (treatment, visit), the subgroup variable, continuous covariate (baseline value), and interaction (treatment by visit, treatment by subgroup).
Standardized effect size (d) = LS mean difference/estimated pooled standard deviation with the small sample bias correction.

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Alnylam Pharmaceuticals Inc.
ALN-TTRSC02-002

Table 14.2
Cardiac Biomarkers - Troponin I (ng/L): Change from Baseline to Month 18, MMRM Model
Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A) Subgroup Analysis
mITT Population

Subgroup Visit	LS Mean (95% CI) Vutrisiran (HELIOS-A) (N=122)	LS Mean (95% CI) Patisiran (HELIOS-A) (N=42)	LS Mean Difference (Vutrisiran-Patisiran) (95% CI), p-value	Standardized Effect Size (95% CI)
Region				
North America	27	8		
Week 12	4.15 (-9.66, 17.96)	43.98 (18.99, 68.96)	-39.82 (-68.41, -11.24), 0.0065	-1.14 (-1.95, -0.32)
Week 24	4.10 (-9.72, 17.92)	28.12 (2.97, 53.27)	-24.02 (-52.74, 4.70), 0.1009	-0.93 (-1.78, -0.08)
Month 9	3.74 (-10.12, 17.60)	49.94 (24.89, 74.99)	-46.20 (-74.85, -17.54), 0.0017	-1.85 (-2.81, -0.90)
Week 48	2.08 (-11.80, 15.97)	24.51 (-0.49, 49.50)	-22.42 (-51.04, 6.20), 0.1242	-0.72 (-1.52, 0.08)
Week 60	4.12 (-9.69, 17.94)	38.42 (13.23, 63.62)	-34.30 (-63.07, -5.54), 0.0196	-2.15 (-3.11, -1.19)
Week 72	3.64 (-10.21, 17.50)	32.71 (7.33, 58.10)	-29.07 (-58.02, -0.12), 0.0491	-0.43 (-1.46, 0.61)
Month 18	1.81 (-12.06, 15.68)	55.80 (30.55, 81.05)	-53.99 (-82.82, -25.15), 0.0003	-0.54 (-1.37, 0.29)
Western Europe	40	19		
Week 12	0.50 (-11.65, 12.65)	15.52 (-3.46, 34.50)	-15.03 (-37.55, 7.50), 0.1905	-0.43 (-0.99, 0.12)
Week 24	0.45 (-11.70, 12.60)	-0.33 (-19.60, 18.93)	0.78 (-21.99, 23.55), 0.9463	0.02 (-0.57, 0.61)
Month 9	0.09 (-12.09, 12.27)	21.49 (2.43, 40.55)	-21.40 (-44.01, 1.21), 0.0636	-0.59 (-1.15, -0.02)
Week 48	-1.57 (-13.73, 10.59)	-3.95 (-23.15, 15.26)	2.38 (-20.35, 25.10), 0.8371	0.05 (-0.50, 0.60)
Week 60	0.47 (-11.66, 12.60)	9.97 (-9.19, 29.13)	-9.50 (-32.17, 13.17), 0.4104	-0.25 (-0.83, 0.32)
Week 72	-0.01 (-12.16, 12.14)	4.26 (-15.01, 23.53)	-4.27 (-27.04, 18.50), 0.7126	-0.12 (-0.67, 0.44)
Month 18	-1.84 (-14.00, 10.32)	27.35 (8.27, 46.42)	-29.19 (-51.80, -6.58), 0.0115	-0.60 (-1.17, -0.02)

LS estimates and p-value derived from mixed-effects model for repeated measures (MMRM), controlling for categorical factors (treatment, visit), the subgroup variable, continuous covariate (baseline value), and interaction (treatment by visit, treatment by subgroup).
Standardized effect size (d) = LS mean difference/estimated pooled standard deviation with the small sample bias correction.

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Table 14.2
Cardiac Biomarkers - Troponin I (ng/L): Change from Baseline to Month 18, MMRM Model
Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A) Subgroup Analysis
mITT Population

Subgroup Visit	LS Mean (95% CI) Vutrisiran (HELIOS-A) (N=122)	LS Mean (95% CI) Patisiran (HELIOS-A) (N=42)	LS Mean Difference (Vutrisiran-Patisiran) (95% CI), p-value	Standardized Effect Size (95% CI)
Rest of World	53	14		
Week 12	1.79 (-9.35, 12.94)	12.89 (-7.95, 33.72)	-11.09 (-34.78, 12.60), 0.3578	-0.16 (-0.74, 0.42)
Week 24	1.74 (-9.40, 12.89)	-2.97 (-23.87, 17.93)	4.71 (-19.03, 28.46), 0.6965	0.26 (-0.33, 0.84)
Month 9	1.39 (-9.82, 12.60)	18.85 (-2.07, 39.78)	-17.46 (-41.26, 6.34), 0.1499	-0.21 (-0.81, 0.39)
Week 48	-0.27 (-11.48, 10.94)	-6.58 (-27.59, 14.42)	6.31 (-17.56, 30.18), 0.6033	0.08 (-0.52, 0.69)
Week 60	1.77 (-9.41, 12.94)	7.33 (-13.83, 28.49)	-5.57 (-29.56, 18.42), 0.6484	-0.27 (-0.89, 0.35)
Week 72	1.29 (-9.91, 12.48)	1.62 (-19.52, 22.76)	-0.34 (-24.32, 23.65), 0.9781	-0.00 (-0.61, 0.60)
Month 18	-0.54 (-11.74, 10.65)	24.71 (3.64, 45.78)	-25.25 (-49.17, -1.34), 0.0385	-0.75 (-1.39, -0.12)
p-value of Treatment*Region	0.1547			

LS estimates and p-value derived from mixed-effects model for repeated measures (MMRM), controlling for categorical factors (treatment, visit), the subgroup variable, continuous covariate (baseline value), and interaction (treatment by visit, treatment by subgroup).
Standardized effect size (d) = LS mean difference/estimated pooled standard deviation with the small sample bias correction.

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

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Table 14.2
Cardiac Biomarkers - Troponin I (ng/L): Change from Baseline to Month 18, MMRM Model
Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A) Subgroup Analysis
mITT Population

Subgroup Visit	LS Mean (95% CI) Vutrisiran (HELIOS-A) (N=122)	LS Mean (95% CI) Patisiran (HELIOS-A) (N=42)	LS Mean Difference (Vutrisiran-Patisiran) (95% CI), p-value	Standardized Effect Size (95% CI)
Baseline NIS				
<50	78	27		
Week 12	0.90 (-9.25, 11.06)	25.44 (8.01, 42.87)	-24.54 (-44.70, -4.37), 0.0172	-0.76 (-1.21, -0.31)
Week 24	0.85 (-9.31, 11.01)	9.34 (-8.20, 26.88)	-8.48 (-28.75, 11.78), 0.4113	-0.29 (-0.75, 0.16)
Month 9	0.49 (-9.74, 10.71)	31.27 (13.82, 48.73)	-30.79 (-51.02, -10.56), 0.0029	-1.03 (-1.50, -0.56)
Week 48	-1.19 (-11.42, 9.04)	5.68 (-11.70, 23.06)	-6.87 (-27.03, 13.29), 0.5037	-0.16 (-0.60, 0.27)
Week 60	0.86 (-9.32, 11.04)	19.62 (2.04, 37.19)	-18.76 (-39.07, 1.55), 0.0701	-0.64 (-1.10, -0.18)
Week 72	0.38 (-9.84, 10.59)	13.50 (-4.09, 31.10)	-13.13 (-33.47, 7.22), 0.2055	-0.26 (-0.72, 0.21)
Month 18	-1.46 (-11.67, 8.76)	36.94 (19.40, 54.48)	-38.40 (-58.69, -18.10), 0.0002	-0.55 (-1.00, -0.09)
≥50	42	14		
Week 12	3.98 (-8.01, 15.98)	9.96 (-11.11, 31.03)	-5.97 (-30.34, 18.40), 0.6301	-0.08 (-0.68, 0.52)
Week 24	3.94 (-8.06, 15.93)	-6.14 (-27.57, 15.28)	10.08 (-14.60, 34.76), 0.4225	0.49 (-0.17, 1.16)
Month 9	3.57 (-8.47, 15.60)	15.79 (-5.47, 37.06)	-12.23 (-36.78, 12.33), 0.3282	-0.13 (-0.75, 0.49)
Week 48	1.90 (-10.13, 13.92)	-9.80 (-31.44, 11.84)	11.69 (-13.19, 36.58), 0.3559	0.15 (-0.49, 0.78)
Week 60	3.94 (-8.04, 15.92)	4.14 (-17.39, 25.67)	-0.20 (-24.96, 24.56), 0.9874	-0.01 (-0.66, 0.64)
Week 72	3.46 (-8.54, 15.46)	-1.98 (-23.74, 19.79)	5.44 (-19.54, 30.41), 0.6689	0.08 (-0.56, 0.71)
Month 18	1.62 (-10.38, 13.63)	21.46 (0.04, 42.88)	-19.83 (-44.51, 4.85), 0.1149	-0.96 (-1.65, -0.28)
p-value of Treatment*Baseline NIS	0.1244			

LS estimates and p-value derived from mixed-effects model for repeated measures (MMRM), controlling for categorical factors (treatment, visit), the subgroup variable, continuous covariate (baseline value), and interaction (treatment by visit, treatment by subgroup).
Standardized effect size (d) = LS mean difference/estimated pooled standard deviation with the small sample bias correction.

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Table 14.2
Cardiac Biomarkers - Troponin I (ng/L): Change from Baseline to Month 18, MMRM Model
Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A) Subgroup Analysis
mITT Population

Subgroup Visit	LS Mean (95% CI) Vutrisiran (HELIOS-A) (N=122)	LS Mean (95% CI) Patisiran (HELIOS-A) (N=42)	LS Mean Difference (Vutrisiran-Patisiran) (95% CI), p-value	Standardized Effect Size (95% CI)
Previous Tetramer Stabilizer Use				
Yes	74	33		
Week 12	0.84 (-9.41, 11.09)	14.78 (-1.84, 31.41)	-13.94 (-33.52, 5.63), 0.1623	-0.23 (-0.65, 0.18)
Week 24	0.79 (-9.46, 11.05)	-1.09 (-17.93, 15.76)	1.88 (-17.89, 21.64), 0.8519	0.07 (-0.36, 0.49)
Month 9	0.44 (-9.85, 10.74)	20.81 (4.10, 37.52)	-20.37 (-40.04, -0.70), 0.0424	-0.29 (-0.71, 0.12)
Week 48	-1.23 (-11.51, 9.06)	-4.67 (-21.53, 12.19)	3.45 (-16.35, 23.24), 0.7325	0.05 (-0.37, 0.47)
Week 60	0.82 (-9.42, 11.06)	9.32 (-7.58, 26.22)	-8.50 (-28.30, 11.30), 0.3995	-0.27 (-0.70, 0.15)
Week 72	0.34 (-9.93, 10.61)	3.50 (-13.48, 20.48)	-3.16 (-23.05, 16.73), 0.7550	-0.05 (-0.48, 0.38)
Month 18	-1.50 (-11.78, 8.78)	26.62 (9.82, 43.43)	-28.12 (-47.86, -8.38), 0.0053	-0.64 (-1.08, -0.20)
No	46	8		
Week 12	3.55 (-8.04, 15.14)	42.47 (17.56, 67.39)	-38.92 (-66.43, -11.42), 0.0057	-1.32 (-2.10, -0.54)
Week 24	3.50 (-8.10, 15.10)	26.60 (1.52, 51.68)	-23.10 (-50.76, 4.56), 0.1013	-1.06 (-1.88, -0.25)
Month 9	3.15 (-8.52, 14.82)	48.50 (23.48, 73.52)	-45.35 (-72.98, -17.72), 0.0014	-2.15 (-3.11, -1.19)
Week 48	1.48 (-10.19, 13.16)	23.02 (-1.91, 47.94)	-21.53 (-49.08, 6.02), 0.1251	-0.79 (-1.54, -0.03)
Week 60	3.53 (-8.10, 15.16)	37.01 (11.84, 62.18)	-33.48 (-61.23, -5.73), 0.0182	-2.08 (-3.01, -1.15)
Week 72	3.05 (-8.61, 14.70)	31.19 (5.88, 56.49)	-28.14 (-56.02, -0.26), 0.0479	-0.54 (-1.39, 0.31)
Month 18	1.21 (-10.45, 12.87)	54.31 (29.13, 79.49)	-53.10 (-80.87, -25.33), 0.0002	-0.67 (-1.47, 0.13)
p-value of Treatment*Previous Tetramer Stabilizer Use	0.0637			

LS estimates and p-value derived from mixed-effects model for repeated measures (MMRM), controlling for categorical factors (treatment, visit), the subgroup variable, continuous covariate (baseline value), and interaction (treatment by visit, treatment by subgroup).
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Table 14.2
Cardiac Biomarkers - Troponin I (ng/L): Change from Baseline to Month 18, MMRM Model
Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A) Subgroup Analysis
mITT Population

Subgroup Visit	LS Mean (95% CI) Vutrisiran (HELIOS-A) (N=122)	LS Mean (95% CI) Patisiran (HELIOS-A) (N=42)	LS Mean Difference (Vutrisiran-Patisiran) (95% CI), p-value	Standardized Effect Size (95% CI)
Genotype				
V30M	53	20		
Week 12	3.20 (-7.95, 14.35)	7.30 (-11.33, 25.93)	-4.10 (-25.75, 17.55), 0.7100	-0.14 (-0.66, 0.38)
Week 24	3.15 (-8.00, 14.30)	-8.37 (-27.12, 10.39)	11.52 (-10.24, 33.28), 0.2987	0.39 (-0.17, 0.94)
Month 9	2.78 (-8.40, 13.96)	13.48 (-5.16, 32.12)	-10.70 (-32.38, 10.98), 0.3326	-0.35 (-0.88, 0.17)
Week 48	1.11 (-10.07, 12.30)	-11.29 (-29.85, 7.26)	12.41 (-9.20, 34.02), 0.2598	0.41 (-0.10, 0.93)
Week 60	3.16 (-7.98, 14.29)	2.23 (-16.49, 20.95)	0.93 (-20.80, 22.65), 0.9333	0.07 (-0.47, 0.61)
Week 72	2.68 (-8.48, 13.83)	-3.37 (-22.06, 15.32)	6.05 (-15.66, 27.76), 0.5843	0.74 (0.20, 1.27)
Month 18	0.83 (-10.32, 11.99)	19.52 (0.88, 38.17)	-18.69 (-40.35, 2.97), 0.0907	-0.61 (-1.14, -0.08)
non-V30M	67	21		
Week 12	0.44 (-9.98, 10.87)	32.92 (14.38, 51.46)	-32.47 (-53.81, -11.14), 0.0029	-0.50 (-1.00, -0.01)
Week 24	0.39 (-10.04, 10.83)	17.25 (-1.57, 36.07)	-16.86 (-38.44, 4.73), 0.1256	-0.72 (-1.23, -0.20)
Month 9	0.02 (-10.48, 10.53)	39.10 (20.38, 57.81)	-39.07 (-60.60, -17.55), 0.0004	-0.51 (-1.03, 0.00)
Week 48	-1.64 (-12.14, 8.85)	14.32 (-4.65, 33.29)	-15.97 (-37.71, 5.78), 0.1497	-0.22 (-0.73, 0.29)
Week 60	0.40 (-10.06, 10.85)	27.85 (8.87, 46.83)	-27.45 (-49.19, -5.71), 0.0134	-0.84 (-1.37, -0.31)
Week 72	-0.08 (-10.57, 10.41)	22.25 (3.04, 41.46)	-22.33 (-44.28, -0.38), 0.0462	-0.28 (-0.82, 0.27)
Month 18	-1.92 (-12.42, 8.57)	45.14 (26.21, 64.07)	-47.07 (-68.78, -25.35), 2.483E-05	-0.63 (-1.17, -0.09)
p-value of Treatment*Genotype	0.0119			

LS estimates and p-value derived from mixed-effects model for repeated measures (MMRM), controlling for categorical factors (treatment, visit), the subgroup variable, continuous covariate (baseline value), and interaction (treatment by visit, treatment by subgroup).
Standardized effect size (d) = LS mean difference/estimated pooled standard deviation with the small sample bias correction.

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Table 14.2
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Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A) Subgroup Analysis
mITT Population

Subgroup Visit	LS Mean (95% CI) Vutrisiran (HELIOS-A) (N=122)	LS Mean (95% CI) Patisiran (HELIOS-A) (N=42)	LS Mean Difference (Vutrisiran-Patisiran) (95% CI), p-value	Standardized Effect Size (95% CI)
FAP Stage				
I	84	30		
Week 12	2.48 (-7.53, 12.48)	16.01 (-1.07, 33.09)	-13.53 (-33.38, 6.31), 0.1810	-0.24 (-0.66, 0.18)
Week 24	2.43 (-7.58, 12.44)	0.35 (-16.84, 17.54)	2.08 (-17.87, 22.02), 0.8380	0.08 (-0.35, 0.51)
Month 9	2.07 (-8.00, 12.14)	22.12 (5.01, 39.23)	-20.05 (-39.95, -0.14), 0.0484	-0.29 (-0.72, 0.13)
Week 48	0.41 (-9.67, 10.49)	-2.74 (-19.78, 14.29)	3.15 (-16.69, 22.99), 0.7552	0.05 (-0.37, 0.47)
Week 60	2.45 (-7.58, 12.48)	10.84 (-6.36, 28.03)	-8.39 (-28.34, 11.57), 0.4093	-0.29 (-0.72, 0.14)
Week 72	1.97 (-8.08, 12.02)	5.22 (-11.94, 22.38)	-3.25 (-23.19, 16.68), 0.7488	-0.06 (-0.49, 0.38)
Month 18	0.13 (-9.92, 10.18)	28.10 (10.98, 45.22)	-27.97 (-47.87, -8.08), 0.0059	-0.68 (-1.12, -0.24)
II&III	36	11		
Week 12	0.47 (-12.10, 13.04)	31.62 (8.92, 54.32)	-31.15 (-57.12, -5.18), 0.0189	-0.86 (-1.55, -0.17)
Week 24	0.42 (-12.15, 12.99)	15.96 (-7.14, 39.07)	-15.54 (-41.87, 10.79), 0.2464	-0.56 (-1.32, 0.21)
Month 9	0.07 (-12.54, 12.67)	37.73 (14.81, 60.65)	-37.66 (-63.84, -11.49), 0.0049	-1.53 (-2.32, -0.73)
Week 48	-1.60 (-14.18, 10.98)	12.87 (-10.51, 36.24)	-14.47 (-41.03, 12.10), 0.2848	-0.43 (-1.15, 0.30)
Week 60	0.45 (-12.10, 12.99)	26.45 (3.15, 49.75)	-26.00 (-52.49, 0.48), 0.0542	-1.26 (-2.06, -0.46)
Week 72	-0.04 (-12.62, 12.55)	20.83 (-2.87, 44.53)	-20.87 (-47.72, 5.98), 0.1273	-0.35 (-1.10, 0.41)
Month 18	-1.88 (-14.48, 10.73)	43.71 (20.45, 66.98)	-45.59 (-72.07, -19.11), 0.0008	-0.51 (-1.27, 0.26)
p-value of Treatment*FAP Stage	0.1696			

LS estimates and p-value derived from mixed-effects model for repeated measures (MMRM), controlling for categorical factors (treatment, visit), the subgroup variable, continuous covariate (baseline value), and interaction (treatment by visit, treatment by subgroup).
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Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A) Subgroup Analysis
mITT Population

Subgroup Visit	LS Mean (95% CI) Vutrisiran (HELIOS-A) (N=122)	LS Mean (95% CI) Patisiran (HELIOS-A) (N=42)	LS Mean Difference (Vutrisiran-Patisiran) (95% CI), p-value	Standardized Effect Size (95% CI)
Cardiac Subpopulation				
Yes	39	14		
Week 12	0.58 (-11.52, 12.68)	40.67 (19.51, 61.82)	-40.08 (-64.51, -15.66), 0.0014	-0.49 (-1.11, 0.14)
Week 24	0.54 (-11.57, 12.64)	24.47 (3.28, 45.66)	-23.93 (-48.39, 0.52), 0.0551	-0.88 (-1.54, -0.22)
Month 9	0.18 (-11.97, 12.32)	46.32 (25.22, 67.41)	-46.14 (-70.54, -21.75), 0.0002	-0.48 (-1.10, 0.15)
Week 48	-1.49 (-13.63, 10.65)	21.18 (-0.03, 42.38)	-22.67 (-47.16, 1.81), 0.0694	-0.25 (-0.88, 0.37)
Week 60	0.55 (-11.57, 12.67)	34.99 (13.66, 56.33)	-34.45 (-59.04, -9.86), 0.0062	-0.83 (-1.49, -0.18)
Week 72	0.07 (-12.07, 12.21)	28.85 (7.53, 50.18)	-28.78 (-53.38, -4.19), 0.0219	-0.28 (-0.91, 0.34)
Month 18	-1.77 (-13.90, 10.37)	52.21 (30.95, 73.48)	-53.98 (-78.52, -29.45), 1.962E-05	-0.57 (-1.25, 0.10)
No	81	27		
Week 12	2.01 (-8.01, 12.02)	10.62 (-6.58, 27.81)	-8.61 (-28.46, 11.24), 0.3945	-0.33 (-0.76, 0.11)
Week 24	1.96 (-8.06, 11.98)	-5.58 (-23.08, 11.91)	7.54 (-12.58, 27.65), 0.4619	0.29 (-0.16, 0.75)
Month 9	1.60 (-8.48, 11.68)	16.27 (-1.10, 33.64)	-14.67 (-34.71, 5.37), 0.1509	-0.56 (-1.02, -0.11)
Week 48	-0.07 (-10.15, 10.00)	-8.87 (-26.31, 8.57)	8.80 (-11.30, 28.90), 0.3901	0.28 (-0.16, 0.72)
Week 60	1.97 (-8.04, 11.98)	4.94 (-12.57, 22.45)	-2.97 (-23.10, 17.15), 0.7717	-0.23 (-0.69, 0.23)
Week 72	1.49 (-8.56, 11.54)	-1.20 (-18.86, 16.47)	2.69 (-17.58, 22.96), 0.7945	0.26 (-0.21, 0.73)
Month 18	-0.35 (-10.41, 9.72)	22.16 (4.72, 39.61)	-22.51 (-42.60, -2.42), 0.0282	-0.83 (-1.29, -0.36)
p-value of Treatment*Cardiac Subpopulation	0.0089			

LS estimates and p-value derived from mixed-effects model for repeated measures (MMRM), controlling for categorical factors (treatment, visit), the subgroup variable, continuous covariate (baseline value), and interaction (treatment by visit, treatment by subgroup).
Standardized effect size (d) = LS mean difference/estimated pooled standard deviation with the small sample bias correction.

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Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A) Subgroup Analysis
mITT Population

Subgroup Visit	LS Mean (95% CI) Vutrisiran (HELIOS-A) (N=122)	LS Mean (95% CI) Patisiran (HELIOS-A) (N=42)	LS Mean Difference (Vutrisiran-Patisiran) (95% CI), p-value	Standardized Effect Size (95% CI)
Weight (kg)				
<65	45	15		
Week 12	0.13 (-11.59, 11.86)	11.18 (-9.22, 31.58)	-11.05 (-34.63, 12.53), 0.3575	-0.15 (-0.73, 0.43)
Week 24	0.09 (-11.64, 11.82)	-4.67 (-25.21, 15.88)	4.75 (-18.95, 28.46), 0.6936	0.24 (-0.39, 0.87)
Month 9	-0.27 (-12.05, 11.50)	17.13 (-3.36, 37.62)	-17.41 (-41.09, 6.28), 0.1493	-0.20 (-0.79, 0.40)
Week 48	-1.95 (-13.72, 9.83)	-7.92 (-28.32, 12.49)	5.97 (-17.64, 29.58), 0.6193	0.08 (-0.50, 0.66)
Week 60	0.10 (-11.65, 11.84)	5.72 (-14.84, 26.29)	-5.63 (-29.36, 18.11), 0.6413	-0.25 (-0.87, 0.36)
Week 72	-0.38 (-12.14, 11.39)	-0.10 (-20.64, 20.45)	-0.28 (-24.01, 23.44), 0.9814	-0.00 (-0.61, 0.61)
Month 18	-2.21 (-13.97, 9.55)	23.01 (2.53, 43.49)	-25.22 (-48.89, -1.56), 0.0368	-0.71 (-1.32, -0.10)
≥65	75	26		
Week 12	3.03 (-7.24, 13.30)	25.37 (7.84, 42.91)	-22.34 (-42.67, -2.01), 0.0313	-0.69 (-1.15, -0.23)
Week 24	2.99 (-7.29, 13.26)	9.53 (-8.25, 27.30)	-6.54 (-27.08, 14.00), 0.5319	-0.22 (-0.68, 0.24)
Month 9	2.63 (-7.71, 12.96)	31.33 (13.70, 48.95)	-28.70 (-49.14, -8.26), 0.0060	-0.93 (-1.41, -0.45)
Week 48	0.95 (-9.37, 11.28)	6.28 (-11.55, 24.10)	-5.32 (-25.93, 15.28), 0.6120	-0.14 (-0.59, 0.32)
Week 60	3.00 (-7.27, 13.27)	19.92 (2.05, 37.78)	-16.92 (-37.53, 3.69), 0.1075	-0.59 (-1.07, -0.12)
Week 72	2.52 (-7.78, 12.83)	14.10 (-3.94, 32.14)	-11.57 (-32.36, 9.21), 0.2744	-0.25 (-0.72, 0.23)
Month 18	0.69 (-9.63, 11.00)	37.20 (19.38, 55.02)	-36.51 (-57.11, -15.92), 0.0005	-0.53 (-1.01, -0.05)
p-value of Treatment*Weight	0.3313			

LS estimates and p-value derived from mixed-effects model for repeated measures (MMRM), controlling for categorical factors (treatment, visit), the subgroup variable, continuous covariate (baseline value), and interaction (treatment by visit, treatment by subgroup).
Standardized effect size (d) = LS mean difference/estimated pooled standard deviation with the small sample bias correction.

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Table 14.3
Cardiac Biomarkers - Troponin I (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Age (years): <65

Subgroup Visit	Vutrisiran (HELIOS-A) (N=76)	Patisiran (HELIOS-A) (N=31)
Baseline		
n	76	31
Mean (SD)	23.793 (56.961)	63.232 (223.205)
SE	6.534	40.089
Median	10.000	16.000
Min, Max	10.00, 483.60	10.00, 1262.00
Week 12		
Actual Value		
n	75	31
Mean (SD)	25.403 (74.179)	90.245 (367.365)
SE	8.565	65.981
Median	10.000	15.300
Min, Max	10.00, 647.60	10.00, 2066.80
Change from baseline		
n	75	31
Mean (SD)	1.425 (21.646)	27.013 (144.643)
SE	2.499	25.979
Median	0.000	0.000
Min, Max	-76.60, 164.00	-28.20, 804.80

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Table 14.3
Cardiac Biomarkers - Troponin I (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Age (years): <65

Subgroup Visit	Vutrisiran (HELIOS-A) (N=76)	Patisiran (HELIOS-A) (N=31)
Week 24		
Actual Value		
n	74	28
Mean (SD)	24.162 (68.341)	75.975 (295.382)
SE	7.944	55.822
Median	10.000	12.050
Min, Max	10.00, 591.00	10.00, 1581.30
Change from baseline		
n	74	28
Mean (SD)	0.032 (16.399)	11.379 (60.651)
SE	1.906	11.462
Median	0.000	0.000
Min, Max	-75.00, 107.40	-11.60, 319.30

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Cardiac Biomarkers - Troponin I (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Age (years): <65

Subgroup Visit	Vutrisiran (HELIOS-A) (N=76)	Patisiran (HELIOS-A) (N=31)
Month 9		
Actual Value		
n	73	29
Mean (SD)	24.293 (63.767)	96.507 (401.872)
SE	7.463	74.626
Median	10.000	11.500
Min, Max	10.00, 541.50	10.00, 2183.70
Change from baseline		
n	73	29
Mean (SD)	0.025 (10.838)	32.690 (171.385)
SE	1.268	31.825
Median	0.000	0.000
Min, Max	-43.20, 57.90	-21.10, 921.70

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Table 14.3
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mITT Population

Age (years): <65

Subgroup Visit	Vutrisiran (HELIOS-A) (N=76)	Patisiran (HELIOS-A) (N=31)
Week 48		
Actual Value		
n	73	29
Mean (SD)	21.229 (47.350)	53.138 (177.531)
SE	5.542	32.967
Median	10.000	10.000
Min, Max	10.00, 400.70	10.00, 971.40
Change from baseline		
n	73	29
Mean (SD)	-2.982 (13.642)	-10.352 (55.129)
SE	1.597	10.237
Median	0.000	0.000
Min, Max	-82.90, 27.70	-290.60, 42.20

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Table 14.3
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mITT Population

Age (years): <65

Subgroup Visit	Vutrisiran (HELIOS-A) (N=76)	Patisiran (HELIOS-A) (N=31)
Week 60		
Actual Value		
n	74	27
Mean (SD)	22.896 (58.321)	78.178 (308.599)
SE	6.780	59.390
Median	10.000	10.000
Min, Max	10.00, 499.00	10.00, 1620.80
Change from baseline		
n	74	27
Mean (SD)	-1.180 (7.654)	12.363 (69.796)
SE	0.890	13.432
Median	0.000	0.000
Min, Max	-46.10, 16.70	-27.40, 358.80

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Table 14.3
Cardiac Biomarkers - Troponin I (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Age (years): <65

Subgroup Visit	Vutrisiran (HELIOS-A) (N=76)	Patisiran (HELIOS-A) (N=31)
Week 72		
Actual Value		
n	74	26
Mean (SD)	21.273 (41.928)	58.446 (198.494)
SE	4.874	38.928
Median	10.000	12.800
Min, Max	10.00, 354.80	10.00, 1029.20
Change from baseline		
n	74	26
Mean (SD)	-2.803 (18.503)	-10.588 (46.014)
SE	2.151	9.024
Median	0.000	0.000
Min, Max	-128.80, 18.00	-232.80, 18.80

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Table 14.3
Cardiac Biomarkers - Troponin I (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Age (years): <65

Subgroup Visit	Vutrisiran (HELIOS-A) (N=76)	Patisiran (HELIOS-A) (N=31)
Month 18		
Actual Value		
n	73	28
Mean (SD)	21.326 (43.591)	19.807 (16.548)
SE	5.102	3.127
Median	10.000	10.000
Min, Max	10.00, 366.90	10.00, 83.60
Change from baseline		
n	73	28
Mean (SD)	-2.848 (17.401)	-0.879 (8.527)
SE	2.037	1.611
Median	0.000	0.000
Min, Max	-116.70, 32.80	-22.80, 30.00

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Cardiac Biomarkers - Troponin I (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Age (years): ≥65

Subgroup Visit	Vutrisiran (HELIOS-A) (N=46)	Patisiran (HELIOS-A) (N=11)
Baseline		
n	46	11
Mean (SD)	58.007 (183.489)	81.245 (113.694)
SE	27.054	34.280
Median	16.100	17.900
Min, Max	10.00, 1250.50	10.00, 325.40
Week 12		
Actual Value		
n	44	9
Mean (SD)	23.168 (18.339)	117.767 (176.597)
SE	2.765	58.866
Median	14.600	17.400
Min, Max	10.00, 79.10	10.00, 443.70
Change from baseline		
n	44	9
Mean (SD)	-7.734 (31.085)	22.867 (71.548)
SE	4.686	23.849
Median	0.000	0.000
Min, Max	-195.60, 23.10	-55.30, 191.10

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Table 14.3
Cardiac Biomarkers - Troponin I (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Age (years): ≥65

Subgroup Visit	Vutrisiran (HELIOS-A) (N=46)	Patisiran (HELIOS-A) (N=11)
Week 24		
Actual Value		
n	40	8
Mean (SD)	23.883 (20.352)	114.588 (160.933)
SE	3.218	56.898
Median	14.200	11.550
Min, Max	10.00, 86.10	10.00, 398.30
Change from baseline		
n	40	8
Mean (SD)	-5.713 (32.734)	13.588 (54.629)
SE	5.176	19.314
Median	0.000	0.000
Min, Max	-195.60, 23.60	-32.70, 145.70

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Cardiac Biomarkers - Troponin I (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Age (years): ≥65

Subgroup Visit	Vutrisiran (HELIOS-A) (N=46)	Patisiran (HELIOS-A) (N=11)
Month 9		
Actual Value		
n	39	9
Mean (SD)	23.879 (19.819)	89.500 (158.312)
SE	3.174	52.771
Median	14.700	14.500
Min, Max	10.00, 82.70	10.00, 481.40
Change from baseline		
n	39	9
Mean (SD)	-6.585 (33.447)	19.456 (52.666)
SE	5.356	17.555
Median	0.000	0.000
Min, Max	-195.60, 29.30	-17.60, 156.00

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Table 14.3
Cardiac Biomarkers - Troponin I (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Age (years): ≥65

Subgroup Visit	Vutrisiran (HELIOS-A) (N=46)	Patisiran (HELIOS-A) (N=11)
Week 48		
Actual Value		
n	41	10
Mean (SD)	25.651 (21.420)	142.460 (217.566)
SE	3.345	68.800
Median	15.000	17.400
Min, Max	10.00, 78.30	10.00, 605.40
Change from baseline		
n	41	10
Mean (SD)	-6.263 (32.633)	54.160 (105.026)
SE	5.096	33.212
Median	0.000	0.000
Min, Max	-195.60, 34.80	-24.10, 280.00

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Table 14.3
Cardiac Biomarkers - Troponin I (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Age (years): ≥65

Subgroup Visit	Vutrisiran (HELIOS-A) (N=46)	Patisiran (HELIOS-A) (N=11)
Week 60		
Actual Value		
n	44	8
Mean (SD)	27.523 (29.056)	133.475 (232.524)
SE	4.380	82.210
Median	14.650	17.450
Min, Max	10.00, 153.70	10.00, 635.80
Change from baseline		
n	44	8
Mean (SD)	-3.380 (12.781)	45.375 (112.074)
SE	1.927	39.624
Median	0.000	0.000
Min, Max	-51.90, 17.40	-20.20, 310.40

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Table 14.3
Cardiac Biomarkers - Troponin I (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Age (years): ≥65

Subgroup Visit	Vutrisiran (HELIOS-A) (N=46)	Patisiran (HELIOS-A) (N=11)
Week 72		
Actual Value		
n	40	9
Mean (SD)	25.638 (23.036)	156.233 (281.596)
SE	3.642	93.865
Median	14.500	16.900
Min, Max	10.00, 96.30	10.00, 665.40
Change from baseline		
n	40	9
Mean (SD)	-0.405 (11.486)	76.811 (164.741)
SE	1.816	54.914
Median	0.000	0.000
Min, Max	-31.10, 34.00	-25.10, 412.80

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Table 14.3
Cardiac Biomarkers - Troponin I (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Age (years): ≥65

Subgroup Visit	Vutrisiran (HELIOS-A) (N=46)	Patisiran (HELIOS-A) (N=11)
Month 18		
Actual Value		
n	39	8
Mean (SD)	23.392 (21.963)	200.113 (348.021)
SE	3.517	123.044
Median	14.400	17.900
Min, Max	10.00, 93.70	10.00, 871.30
Change from baseline		
n	39	8
Mean (SD)	-7.923 (33.665)	112.013 (233.387)
SE	5.391	82.515
Median	0.000	0.000
Min, Max	-195.60, 45.50	-28.10, 618.70

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Table 14.3
Cardiac Biomarkers - Troponin I (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Sex: Male

Subgroup Visit	Vutrisiran (HELIOS-A) (N=79)	Patisiran (HELIOS-A) (N=27)
Baseline		
n	79	27
Mean (SD)	45.491 (148.970)	47.556 (77.691)
SE	16.760	14.952
Median	12.700	17.900
Min, Max	10.00, 1250.50	10.00, 325.40
Week 12		
Actual Value		
n	76	25
Mean (SD)	30.226 (73.989)	59.308 (112.808)
SE	8.487	22.562
Median	12.300	17.400
Min, Max	10.00, 647.60	10.00, 443.70
Change from baseline		
n	76	25
Mean (SD)	0.289 (22.625)	9.532 (43.627)
SE	2.595	8.725
Median	0.000	0.000
Min, Max	-76.60, 164.00	-55.30, 191.10

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Table 14.3
Cardiac Biomarkers - Troponin I (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Sex: Male

Subgroup Visit	Vutrisiran (HELIOS-A) (N=79)	Patisiran (HELIOS-A) (N=27)
Week 24		
Actual Value		
n	73	24
Mean (SD)	28.992 (69.131)	53.038 (100.061)
SE	8.091	20.425
Median	10.900	13.400
Min, Max	10.00, 591.00	10.00, 398.30
Change from baseline		
n	73	24
Mean (SD)	0.134 (17.870)	4.850 (31.153)
SE	2.092	6.359
Median	0.000	0.000
Min, Max	-75.00, 107.40	-32.70, 145.70

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Cardiac Biomarkers - Troponin I (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Sex: Male

Subgroup Visit	Vutrisiran (HELIOS-A) (N=79)	Patisiran (HELIOS-A) (N=27)
Month 9		
Actual Value		
n	72	24
Mean (SD)	29.874 (64.650)	47.121 (100.341)
SE	7.619	20.482
Median	12.650	13.450
Min, Max	10.00, 541.50	10.00, 481.40
Change from baseline		
n	72	24
Mean (SD)	0.361 (13.329)	8.254 (33.666)
SE	1.571	6.872
Median	0.000	0.000
Min, Max	-43.20, 57.90	-21.10, 156.00

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Table 14.3
Cardiac Biomarkers - Troponin I (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Sex: Male

Subgroup Visit	Vutrisiran (HELIOS-A) (N=79)	Patisiran (HELIOS-A) (N=27)
Week 48		
Actual Value		
n	74	24
Mean (SD)	27.401 (48.372)	70.746 (150.321)
SE	5.623	30.684
Median	11.950	10.500
Min, Max	10.00, 400.70	10.00, 605.40
Change from baseline		
n	74	24
Mean (SD)	-2.788 (15.696)	22.650 (71.882)
SE	1.825	14.673
Median	0.000	0.000
Min, Max	-82.90, 34.80	-28.00, 280.00

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Table 14.3
Cardiac Biomarkers - Troponin I (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Sex: Male

Subgroup Visit	Vutrisiran (HELIOS-A) (N=79)	Patisiran (HELIOS-A) (N=27)
Week 60		
Actual Value		
n	76	22
Mean (SD)	28.317 (58.576)	60.832 (146.107)
SE	6.719	31.150
Median	10.900	11.350
Min, Max	10.00, 499.00	10.00, 635.80
Change from baseline		
n	76	22
Mean (SD)	-1.620 (10.044)	16.464 (68.962)
SE	1.152	14.703
Median	0.000	0.000
Min, Max	-46.10, 17.40	-27.40, 310.40

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Table 14.3
Cardiac Biomarkers - Troponin I (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Sex: Male

Subgroup Visit	Vutrisiran (HELIOS-A) (N=79)	Patisiran (HELIOS-A) (N=27)
Week 72		
Actual Value		
n	75	23
Mean (SD)	26.364 (43.443)	73.491 (183.309)
SE	5.016	38.223
Median	10.000	14.400
Min, Max	10.00, 354.80	10.00, 665.40
Change from baseline		
n	75	23
Mean (SD)	-2.891 (19.730)	30.617 (106.401)
SE	2.278	22.186
Median	0.000	0.000
Min, Max	-128.80, 34.00	-22.40, 412.80

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Table 14.3
Cardiac Biomarkers - Troponin I (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Sex: Male

Subgroup Visit	Vutrisiran (HELIOS-A) (N=79)	Patisiran (HELIOS-A) (N=27)
Month 18		
Actual Value		
n	73	22
Mean (SD)	26.241 (45.343)	84.282 (220.220)
SE	5.307	46.951
Median	10.000	12.500
Min, Max	10.00, 366.90	10.00, 871.30
Change from baseline		
n	73	22
Mean (SD)	-3.210 (19.241)	39.914 (145.855)
SE	2.252	31.096
Median	0.000	0.000
Min, Max	-116.70, 45.50	-22.80, 618.70

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Table 14.3
Cardiac Biomarkers - Troponin I (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Sex: Female

Subgroup Visit	Vutrisiran (HELIOS-A) (N=43)	Patisiran (HELIOS-A) (N=15)
Baseline		
n	43	15
Mean (SD)	20.530 (32.225)	104.660 (320.505)
SE	4.914	82.754
Median	10.000	16.000
Min, Max	10.00, 205.60	10.00, 1262.00
Week 12		
Actual Value		
n	43	15
Mean (SD)	14.591 (10.340)	158.320 (528.215)
SE	1.577	136.384
Median	10.000	14.500
Min, Max	10.00, 57.80	10.00, 2066.80
Change from baseline		
n	43	15
Mean (SD)	-5.940 (30.508)	53.660 (207.844)
SE	4.652	53.665
Median	0.000	0.000
Min, Max	-195.60, 8.50	-8.20, 804.80

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

Alnylam Pharmaceuticals Inc.
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Table 14.3
Cardiac Biomarkers - Troponin I (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Sex: Female

Subgroup Visit	Vutrisiran (HELIOS-A) (N=43)	Patisiran (HELIOS-A) (N=15)
Week 24		
Actual Value		
n	41	12
Mean (SD)	15.290 (14.215)	147.592 (451.717)
SE	2.220	130.399
Median	10.000	11.000
Min, Max	10.00, 78.50	10.00, 1581.30
Change from baseline		
n	41	12
Mean (SD)	-5.754 (30.974)	25.908 (92.624)
SE	4.837	26.738
Median	0.000	0.000
Min, Max	-195.60, 23.60	-11.60, 319.30

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

Alnylam Pharmaceuticals Inc.
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Table 14.3
Cardiac Biomarkers - Troponin I (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Sex: Female

Subgroup Visit	Vutrisiran (HELIOS-A) (N=43)	Patisiran (HELIOS-A) (N=15)
Month 9		
Actual Value		
n	40	14
Mean (SD)	13.845 (10.541)	176.664 (577.988)
SE	1.667	154.474
Median	10.000	12.700
Min, Max	10.00, 67.00	10.00, 2183.70
Change from baseline		
n	40	14
Mean (SD)	-7.025 (31.239)	66.071 (246.547)
SE	4.939	65.892
Median	0.000	0.000
Min, Max	-195.60, 6.00	-17.60, 921.70

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

Alnylam Pharmaceuticals Inc.
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Table 14.3
Cardiac Biomarkers - Troponin I (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Sex: Female

Subgroup Visit	Vutrisiran (HELIOS-A) (N=43)	Patisiran (HELIOS-A) (N=15)
Week 48		
Actual Value		
n	40	15
Mean (SD)	14.343 (11.380)	84.513 (245.874)
SE	1.799	63.484
Median	10.000	14.200
Min, Max	10.00, 70.90	10.00, 971.40
Change from baseline		
n	40	15
Mean (SD)	-6.705 (31.172)	-20.147 (75.389)
SE	4.929	19.465
Median	0.000	0.000
Min, Max	-195.60, 12.80	-290.60, 20.10

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

Alnylam Pharmaceuticals Inc.
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Table 14.3
Cardiac Biomarkers - Troponin I (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Sex: Female

Subgroup Visit	Vutrisiran (HELIOS-A) (N=43)	Patisiran (HELIOS-A) (N=15)
Week 60		
Actual Value		
n	42	13
Mean (SD)	17.933 (24.664)	141.562 (444.585)
SE	3.806	123.306
Median	10.000	14.800
Min, Max	10.00, 153.70	10.00, 1620.80
Change from baseline		
n	42	13
Mean (SD)	-2.688 (9.674)	25.738 (100.307)
SE	1.493	27.820
Median	0.000	0.000
Min, Max	-51.90, 14.20	-20.20, 358.80

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

Alnylam Pharmaceuticals Inc.
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Table 14.3
Cardiac Biomarkers - Troponin I (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Sex: Female

Subgroup Visit	Vutrisiran (HELIOS-A) (N=43)	Patisiran (HELIOS-A) (N=15)
Week 72		
Actual Value		
n	39	12
Mean (SD)	15.959 (13.652)	102.950 (291.891)
SE	2.186	84.262
Median	10.000	16.700
Min, Max	10.00, 78.90	10.00, 1029.20
Change from baseline		
n	39	12
Mean (SD)	-0.174 (5.832)	-24.017 (66.411)
SE	0.934	19.171
Median	0.000	0.000
Min, Max	-18.10, 14.60	-232.80, 3.00

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

Alnylam Pharmaceuticals Inc.
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Table 14.3
Cardiac Biomarkers - Troponin I (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Sex: Female

Subgroup Visit	Vutrisiran (HELIOS-A) (N=43)	Patisiran (HELIOS-A) (N=15)
Month 18		
Actual Value		
n	39	14
Mean (SD)	14.192 (9.641)	21.521 (20.332)
SE	1.544	5.434
Median	10.000	12.100
Min, Max	10.00, 56.70	10.00, 83.60
Change from baseline		
n	39	14
Mean (SD)	-7.246 (31.810)	-0.471 (11.926)
SE	5.094	3.187
Median	0.000	0.000
Min, Max	-195.60, 6.70	-28.10, 30.00

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Alnylam Pharmaceuticals Inc.
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Table 14.3
Cardiac Biomarkers - Troponin I (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Race: White

Subgroup Visit	Vutrisiran (HELIOS-A) (N=86)	Patisiran (HELIOS-A) (N=29)
Baseline		
n	86	29
Mean (SD)	34.137 (135.018)	74.224 (235.696)
SE	14.559	43.768
Median	10.000	14.500
Min, Max	10.00, 1250.50	10.00, 1262.00
Week 12		
Actual Value		
n	83	27
Mean (SD)	17.331 (12.860)	112.611 (397.767)
SE	1.412	76.550
Median	10.000	14.500
Min, Max	10.00, 57.80	10.00, 2066.80
Change from baseline		
n	83	27
Mean (SD)	-2.153 (22.663)	34.356 (154.871)
SE	2.488	29.805
Median	0.000	0.000
Min, Max	-195.60, 23.10	-8.90, 804.80

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Alnylam Pharmaceuticals Inc.
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Table 14.3
Cardiac Biomarkers - Troponin I (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Race: White

Subgroup Visit	Vutrisiran (HELIOS-A) (N=86)	Patisiran (HELIOS-A) (N=29)
Week 24		
Actual Value		
n	81	25
Mean (SD)	17.106 (15.301)	95.268 (316.059)
SE	1.700	63.212
Median	10.000	12.000
Min, Max	10.00, 86.10	10.00, 1581.30
Change from baseline		
n	81	25
Mean (SD)	-2.107 (22.505)	12.996 (64.065)
SE	2.501	12.813
Median	0.000	0.000
Min, Max	-195.60, 23.90	-11.60, 319.30

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

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Table 14.3
Cardiac Biomarkers - Troponin I (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Race: White

Subgroup Visit	Vutrisiran (HELIOS-A) (N=86)	Patisiran (HELIOS-A) (N=29)
Month 9		
Actual Value		
n	79	27
Mean (SD)	17.625 (15.260)	120.004 (422.204)
SE	1.717	81.253
Median	10.000	14.500
Min, Max	10.00, 78.20	10.00, 2183.70
Change from baseline		
n	79	27
Mean (SD)	-2.089 (23.511)	41.478 (178.859)
SE	2.645	34.421
Median	0.000	0.000
Min, Max	-195.60, 29.30	-21.10, 921.70

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Table 14.3
Cardiac Biomarkers - Troponin I (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Race: White

Subgroup Visit	Vutrisiran (HELIOS-A) (N=86)	Patisiran (HELIOS-A) (N=29)
Week 48		
Actual Value		
n	80	27
Mean (SD)	17.320 (15.075)	76.419 (212.122)
SE	1.685	40.823
Median	10.000	11.000
Min, Max	10.00, 80.20	10.00, 971.40
Change from baseline		
n	80	27
Mean (SD)	-2.203 (22.913)	-1.756 (80.155)
SE	2.562	15.426
Median	0.000	0.000
Min, Max	-195.60, 30.00	-290.60, 280.00

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Table 14.3
Cardiac Biomarkers - Troponin I (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Race: White

Subgroup Visit	Vutrisiran (HELIOS-A) (N=86)	Patisiran (HELIOS-A) (N=29)
Week 60		
Actual Value		
n	84	24
Mean (SD)	18.065 (19.963)	110.429 (345.735)
SE	2.178	70.573
Median	10.000	11.250
Min, Max	10.00, 153.70	10.00, 1620.80
Change from baseline		
n	84	24
Mean (SD)	-1.306 (7.538)	25.575 (95.909)
SE	0.822	19.577
Median	0.000	0.000
Min, Max	-51.90, 12.20	-27.40, 358.80

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

Alnylam Pharmaceuticals Inc.
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Table 14.3
Cardiac Biomarkers - Troponin I (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Race: White

Subgroup Visit	Vutrisiran (HELIOS-A) (N=86)	Patisiran (HELIOS-A) (N=29)
Week 72		
Actual Value		
n	80	24
Mean (SD)	17.343 (14.623)	87.446 (237.597)
SE	1.635	48.499
Median	10.000	14.650
Min, Max	10.00, 78.90	10.00, 1029.20
Change from baseline		
n	80	24
Mean (SD)	0.978 (7.430)	1.429 (82.124)
SE	0.831	16.763
Median	0.000	0.000
Min, Max	-19.60, 34.00	-232.80, 314.70

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ALN-TTRSC02-002

Table 14.3
Cardiac Biomarkers - Troponin I (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Race: White

Subgroup Visit	Vutrisiran (HELIOS-A) (N=86)	Patisiran (HELIOS-A) (N=29)
Month 18		
Actual Value		
n	79	25
Mean (SD)	16.232 (13.752)	42.600 (124.590)
SE	1.547	24.918
Median	10.000	10.800
Min, Max	10.00, 93.70	10.00, 638.40
Change from baseline		
n	79	25
Mean (SD)	-2.585 (23.880)	9.052 (63.860)
SE	2.687	12.772
Median	0.000	0.000
Min, Max	-195.60, 45.50	-28.10, 313.00

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Alnylam Pharmaceuticals Inc.
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Table 14.3
Cardiac Biomarkers - Troponin I (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Race: All Other Races

Subgroup Visit	Vutrisiran (HELIOS-A) (N=36)	Patisiran (HELIOS-A) (N=13)
Baseline		
n	36	13
Mean (SD)	42.800 (82.895)	53.954 (74.913)
SE	13.816	20.777
Median	13.950	17.900
Min, Max	10.00, 483.60	10.00, 252.60
Week 12		
Actual Value		
n	36	13
Mean (SD)	41.281 (106.076)	62.846 (118.344)
SE	17.679	32.823
Median	14.000	17.400
Min, Max	10.00, 647.60	10.00, 443.70
Change from baseline		
n	36	13
Mean (SD)	-1.519 (32.258)	8.892 (57.318)
SE	5.376	15.897
Median	0.000	0.000
Min, Max	-76.60, 164.00	-55.30, 191.10

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Alnylam Pharmaceuticals Inc.
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Table 14.3
Cardiac Biomarkers - Troponin I (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Race: All Other Races

Subgroup Visit	Vutrisiran (HELIOS-A) (N=36)	Patisiran (HELIOS-A) (N=13)
Week 24		
Actual Value		
n	33	11
Mean (SD)	41.142 (100.751)	60.209 (118.113)
SE	17.539	35.612
Median	13.400	11.100
Min, Max	10.00, 591.00	10.00, 398.30
Change from baseline		
n	33	11
Mean (SD)	-1.679 (26.073)	9.309 (46.510)
SE	4.539	14.023
Median	0.000	0.000
Min, Max	-75.00, 107.40	-32.70, 145.70

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Alnylam Pharmaceuticals Inc.
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Table 14.3
Cardiac Biomarkers - Troponin I (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Race: All Other Races

Subgroup Visit	Vutrisiran (HELIOS-A) (N=36)	Patisiran (HELIOS-A) (N=13)
Month 9		
Actual Value		
n	33	11
Mean (SD)	39.767 (93.227)	33.100 (54.027)
SE	16.229	16.290
Median	11.400	11.900
Min, Max	10.00, 541.50	10.00, 193.00
Change from baseline		
n	33	11
Mean (SD)	-2.727 (16.725)	0.291 (9.093)
SE	2.911	2.742
Median	0.000	0.000
Min, Max	-43.20, 57.90	-10.50, 24.80

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Alnylam Pharmaceuticals Inc.
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Table 14.3
Cardiac Biomarkers - Troponin I (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Race: All Other Races

Subgroup Visit	Vutrisiran (HELIOS-A) (N=36)	Patisiran (HELIOS-A) (N=13)
Week 48		
Actual Value		
n	34	12
Mean (SD)	35.759 (68.363)	75.192 (134.137)
SE	11.724	38.722
Median	11.850	13.850
Min, Max	10.00, 400.70	10.00, 363.80
Change from baseline		
n	34	12
Mean (SD)	-8.774 (20.429)	24.067 (62.329)
SE	3.503	17.993
Median	-0.650	0.000
Min, Max	-82.90, 34.80	-7.90, 195.60

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Alnylam Pharmaceuticals Inc.
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Table 14.3
Cardiac Biomarkers - Troponin I (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Race: All Other Races

Subgroup Visit	Vutrisiran (HELIOS-A) (N=36)	Patisiran (HELIOS-A) (N=13)
Week 60		
Actual Value		
n	34	11
Mean (SD)	40.818 (85.207)	48.027 (97.365)
SE	14.613	29.357
Median	10.950	11.900
Min, Max	10.00, 499.00	10.00, 339.30
Change from baseline		
n	34	11
Mean (SD)	-3.715 (14.118)	7.545 (27.000)
SE	2.421	8.141
Median	0.000	0.000
Min, Max	-46.10, 17.40	-12.30, 86.70

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Alnylam Pharmaceuticals Inc.
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Table 14.3
Cardiac Biomarkers - Troponin I (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Race: All Other Races

Subgroup Visit	Vutrisiran (HELIOS-A) (N=36)	Patisiran (HELIOS-A) (N=13)
Week 72		
Actual Value		
n	34	11
Mean (SD)	35.656 (61.454)	75.182 (195.899)
SE	10.539	59.066
Median	10.050	15.200
Min, Max	10.00, 354.80	10.00, 665.40
Change from baseline		
n	34	11
Mean (SD)	-8.876 (26.748)	34.700 (125.558)
SE	4.587	37.857
Median	0.000	0.000
Min, Max	-128.80, 18.00	-21.40, 412.80

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Table 14.3
Cardiac Biomarkers - Troponin I (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Race: All Other Races

Subgroup Visit	Vutrisiran (HELIOS-A) (N=36)	Patisiran (HELIOS-A) (N=13)
Month 18		
Actual Value		
n	33	11
Mean (SD)	35.964 (64.089)	99.136 (257.011)
SE	11.157	77.492
Median	10.000	14.200
Min, Max	10.00, 366.90	10.00, 871.30
Change from baseline		
n	33	11
Mean (SD)	-9.476 (24.959)	58.655 (185.978)
SE	4.345	56.075
Median	0.000	0.000
Min, Max	-116.70, 22.10	-4.20, 618.70

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Table 14.3
Cardiac Biomarkers - Troponin I (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Region: North America

Subgroup Visit	Vutrisiran (HELIOS-A) (N=27)	Patisiran (HELIOS-A) (N=8)
Baseline		
n	27	8
Mean (SD)	21.300 (23.171)	65.150 (92.752)
SE	4.459	32.793
Median	10.000	20.400
Min, Max	10.00, 111.80	10.00, 252.60
Week 12		
Actual Value		
n	27	8
Mean (SD)	19.900 (17.975)	83.025 (149.778)
SE	3.459	52.955
Median	10.000	19.900
Min, Max	10.00, 72.30	10.00, 443.70
Change from baseline		
n	27	8
Mean (SD)	-1.400 (10.266)	17.875 (72.794)
SE	1.976	25.736
Median	0.000	0.000
Min, Max	-39.50, 20.80	-55.30, 191.10

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

Alnylam Pharmaceuticals Inc.
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Table 14.3
Cardiac Biomarkers - Troponin I (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Region: North America

Subgroup Visit	Vutrisiran (HELIOS-A) (N=27)	Patisiran (HELIOS-A) (N=8)
Week 24		
Actual Value		
n	25	7
Mean (SD)	19.992 (20.036)	91.114 (142.458)
SE	4.007	53.844
Median	10.000	27.200
Min, Max	10.00, 86.10	10.00, 398.30
Change from baseline		
n	25	7
Mean (SD)	-2.104 (10.225)	18.086 (57.941)
SE	2.045	21.899
Median	0.000	0.900
Min, Max	-44.00, 14.20	-32.70, 145.70

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Table 14.3
Cardiac Biomarkers - Troponin I (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Region: North America

Subgroup Visit	Vutrisiran (HELIOS-A) (N=27)	Patisiran (HELIOS-A) (N=8)
Month 9		
Actual Value		
n	22	7
Mean (SD)	16.964 (13.518)	42.300 (67.331)
SE	2.882	25.449
Median	10.000	10.000
Min, Max	10.00, 55.40	10.00, 193.00
Change from baseline		
n	22	7
Mean (SD)	-1.764 (8.417)	3.929 (10.010)
SE	1.795	3.783
Median	0.000	0.000
Min, Max	-23.60, 19.10	-4.50, 24.80

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Alnylam Pharmaceuticals Inc.
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Table 14.3
Cardiac Biomarkers - Troponin I (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Region: North America

Subgroup Visit	Vutrisiran (HELIOS-A) (N=27)	Patisiran (HELIOS-A) (N=8)
Week 48		
Actual Value		
n	24	8
Mean (SD)	18.858 (18.530)	102.513 (159.870)
SE	3.783	56.523
Median	10.000	18.700
Min, Max	10.00, 77.20	10.00, 363.80
Change from baseline		
n	24	8
Mean (SD)	-2.971 (8.509)	37.363 (74.008)
SE	1.737	26.166
Median	0.000	0.050
Min, Max	-34.60, 11.70	-3.50, 195.60

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Table 14.3
Cardiac Biomarkers - Troponin I (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Region: North America

Subgroup Visit	Vutrisiran (HELIOS-A) (N=27)	Patisiran (HELIOS-A) (N=8)
Week 60		
Actual Value		
n	27	7
Mean (SD)	20.393 (22.573)	63.543 (122.106)
SE	4.344	46.152
Median	10.000	10.000
Min, Max	10.00, 99.60	10.00, 339.30
Change from baseline		
n	27	7
Mean (SD)	-0.907 (5.949)	13.114 (32.670)
SE	1.145	12.348
Median	0.000	0.000
Min, Max	-16.00, 10.70	-4.50, 86.70

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Table 14.3
Cardiac Biomarkers - Troponin I (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Region: North America

Subgroup Visit	Vutrisiran (HELIOS-A) (N=27)	Patisiran (HELIOS-A) (N=8)
Week 72		
Actual Value		
n	24	4
Mean (SD)	18.663 (19.688)	181.675 (322.698)
SE	4.019	161.349
Median	10.000	25.650
Min, Max	10.00, 96.30	10.00, 665.40
Change from baseline		
n	24	4
Mean (SD)	-0.971 (7.089)	105.000 (205.229)
SE	1.447	102.615
Median	0.000	3.650
Min, Max	-16.90, 20.80	-0.10, 412.80

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

Alnylam Pharmaceuticals Inc.
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Table 14.3
Cardiac Biomarkers - Troponin I (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Region: North America

Subgroup Visit	Vutrisiran (HELIOS-A) (N=27)	Patisiran (HELIOS-A) (N=8)
Month 18		
Actual Value		
n	24	7
Mean (SD)	15.950 (16.717)	139.014 (323.026)
SE	3.412	122.092
Median	10.000	14.200
Min, Max	10.00, 88.90	10.00, 871.30
Change from baseline		
n	24	7
Mean (SD)	-3.271 (5.907)	88.586 (233.762)
SE	1.206	88.354
Median	0.000	0.000
Min, Max	-22.90, 0.00	-1.10, 618.70

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

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Table 14.3
Cardiac Biomarkers - Troponin I (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Region: Western Europe

Subgroup Visit	Vutrisiran (HELIOS-A) (N=42)	Patisiran (HELIOS-A) (N=20)
Baseline		
n	42	20
Mean (SD)	51.240 (192.788)	40.425 (70.468)
SE	29.748	15.757
Median	10.000	12.300
Min, Max	10.00, 1250.50	10.00, 325.40
Week 12		
Actual Value		
n	39	18
Mean (SD)	15.346 (13.545)	47.822 (91.797)
SE	2.169	21.637
Median	10.000	14.200
Min, Max	10.00, 79.10	10.00, 403.00
Change from baseline		
n	39	18
Mean (SD)	-6.026 (32.621)	5.106 (21.638)
SE	5.223	5.100
Median	0.000	0.000
Min, Max	-195.60, 23.10	-28.20, 77.60

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Table 14.3
Cardiac Biomarkers - Troponin I (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Region: Western Europe

Subgroup Visit	Vutrisiran (HELIOS-A) (N=42)	Patisiran (HELIOS-A) (N=20)
Week 24		
Actual Value		
n	37	15
Mean (SD)	14.124 (12.233)	39.273 (81.960)
SE	2.011	21.162
Median	10.000	10.000
Min, Max	10.00, 78.50	10.00, 329.80
Change from baseline		
n	37	15
Mean (SD)	-5.222 (32.476)	0.520 (5.317)
SE	5.339	1.373
Median	0.000	0.000
Min, Max	-195.60, 10.20	-11.40, 15.70

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Table 14.3
Cardiac Biomarkers - Troponin I (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Region: Western Europe

Subgroup Visit	Vutrisiran (HELIOS-A) (N=42)	Patisiran (HELIOS-A) (N=20)
Month 9		
Actual Value		
n	38	18
Mean (SD)	15.268 (15.106)	47.822 (109.805)
SE	2.450	25.881
Median	10.000	12.250
Min, Max	10.00, 82.70	10.00, 481.40
Change from baseline		
n	38	18
Mean (SD)	-6.179 (32.267)	8.383 (39.076)
SE	5.234	9.210
Median	0.000	0.000
Min, Max	-195.60, 13.90	-21.10, 156.00

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Table 14.3
Cardiac Biomarkers - Troponin I (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Region: Western Europe

Subgroup Visit	Vutrisiran (HELIOS-A) (N=42)	Patisiran (HELIOS-A) (N=20)
Week 48		
Actual Value		
n	39	18
Mean (SD)	14.954 (14.603)	51.500 (139.010)
SE	2.338	32.765
Median	10.000	11.250
Min, Max	10.00, 78.30	10.00, 605.40
Change from baseline		
n	39	18
Mean (SD)	-6.418 (31.699)	12.061 (67.784)
SE	5.076	15.977
Median	0.000	0.000
Min, Max	-195.60, 5.60	-28.00, 280.00

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Table 14.3
Cardiac Biomarkers - Troponin I (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Region: Western Europe

Subgroup Visit	Vutrisiran (HELIOS-A) (N=42)	Patisiran (HELIOS-A) (N=20)
Week 60		
Actual Value		
n	40	16
Mean (SD)	18.400 (25.608)	54.794 (155.191)
SE	4.049	38.798
Median	10.000	11.250
Min, Max	10.00, 153.70	10.00, 635.80
Change from baseline		
n	40	16
Mean (SD)	-2.688 (11.055)	13.713 (79.660)
SE	1.748	19.915
Median	0.000	0.000
Min, Max	-51.90, 12.20	-27.40, 310.40

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Table 14.3
Cardiac Biomarkers - Troponin I (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Region: Western Europe

Subgroup Visit	Vutrisiran (HELIOS-A) (N=42)	Patisiran (HELIOS-A) (N=20)
Week 72		
Actual Value		
n	38	18
Mean (SD)	15.029 (15.771)	52.344 (147.126)
SE	2.558	34.678
Median	10.000	13.050
Min, Max	10.00, 80.30	10.00, 640.10
Change from baseline		
n	38	18
Mean (SD)	-1.271 (5.691)	12.906 (75.883)
SE	0.923	17.886
Median	0.000	0.000
Min, Max	-27.40, 5.50	-25.10, 314.70

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Table 14.3
Cardiac Biomarkers - Troponin I (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Region: Western Europe

Subgroup Visit	Vutrisiran (HELIOS-A) (N=42)	Patisiran (HELIOS-A) (N=20)
Month 18		
Actual Value		
n	38	17
Mean (SD)	15.326 (14.218)	56.959 (151.009)
SE	2.306	36.625
Median	10.000	10.800
Min, Max	10.00, 73.40	10.00, 638.40
Change from baseline		
n	38	17
Mean (SD)	-6.345 (32.967)	15.788 (77.635)
SE	5.348	18.829
Median	0.000	0.000
Min, Max	-195.60, 32.80	-28.10, 313.00

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Table 14.3
Cardiac Biomarkers - Troponin I (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Region: Rest of World

Subgroup Visit	Vutrisiran (HELIOS-A) (N=53)	Patisiran (HELIOS-A) (N=14)
Baseline		
n	53	14
Mean (SD)	33.008 (67.670)	108.871 (332.043)
SE	9.295	88.742
Median	14.800	19.750
Min, Max	10.00, 483.60	10.00, 1262.00
Week 12		
Actual Value		
n	53	14
Mean (SD)	33.751 (87.491)	166.607 (547.039)
SE	12.018	146.202
Median	16.600	17.400
Min, Max	10.00, 647.60	10.00, 2066.80
Change from baseline		
n	53	14
Mean (SD)	0.743 (25.695)	57.736 (215.046)
SE	3.529	57.474
Median	0.000	0.000
Min, Max	-76.60, 164.00	-8.20, 804.80

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Table 14.3
Cardiac Biomarkers - Troponin I (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Region: Rest of World

Subgroup Visit	Vutrisiran (HELIOS-A) (N=53)	Patisiran (HELIOS-A) (N=14)
Week 24		
Actual Value		
n	52	14
Mean (SD)	33.094 (80.898)	129.793 (417.945)
SE	11.219	111.701
Median	14.900	12.350
Min, Max	10.00, 591.00	10.00, 1581.30
Change from baseline		
n	52	14
Mean (SD)	0.379 (20.351)	20.921 (86.092)
SE	2.822	23.009
Median	0.000	-1.200
Min, Max	-75.00, 107.40	-11.60, 319.30

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Table 14.3
Cardiac Biomarkers - Troponin I (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Region: Rest of World

Subgroup Visit	Vutrisiran (HELIOS-A) (N=53)	Patisiran (HELIOS-A) (N=14)
Month 9		
Actual Value		
n	52	13
Mean (SD)	33.679 (74.959)	188.254 (599.871)
SE	10.395	166.374
Median	13.900	15.000
Min, Max	10.00, 541.50	10.00, 2183.70
Change from baseline		
n	52	13
Mean (SD)	0.358 (14.766)	72.669 (255.350)
SE	2.048	70.821
Median	0.000	0.000
Min, Max	-43.20, 57.90	-7.10, 921.70

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Table 14.3
Cardiac Biomarkers - Troponin I (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Region: Rest of World

Subgroup Visit	Vutrisiran (HELIOS-A) (N=53)	Patisiran (HELIOS-A) (N=14)
Week 48		
Actual Value		
n	51	13
Mean (SD)	30.698 (56.273)	93.731 (264.559)
SE	7.880	73.375
Median	14.900	10.000
Min, Max	10.00, 400.70	10.00, 971.40
Change from baseline		
n	51	13
Mean (SD)	-2.998 (17.961)	-21.123 (82.045)
SE	2.515	22.755
Median	0.000	0.000
Min, Max	-82.90, 34.80	-290.60, 42.20

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Table 14.3
Cardiac Biomarkers - Troponin I (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Region: Rest of World

Subgroup Visit	Vutrisiran (HELIOS-A) (N=53)	Patisiran (HELIOS-A) (N=14)
Week 60		
Actual Value		
n	51	12
Mean (SD)	31.739 (69.535)	154.758 (461.979)
SE	9.737	133.362
Median	14.300	13.350
Min, Max	10.00, 499.00	10.00, 1620.80
Change from baseline		
n	51	12
Mean (SD)	-2.039 (10.674)	32.133 (103.128)
SE	1.495	29.771
Median	0.000	0.000
Min, Max	-46.10, 17.40	-6.00, 358.80

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Table 14.3
Cardiac Biomarkers - Troponin I (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Region: Rest of World

Subgroup Visit	Vutrisiran (HELIOS-A) (N=53)	Patisiran (HELIOS-A) (N=14)
Week 72		
Actual Value		
n	52	13
Mean (SD)	30.398 (49.645)	96.677 (280.569)
SE	6.885	77.816
Median	14.200	15.200
Min, Max	10.00, 354.80	10.00, 1029.20
Change from baseline		
n	52	13
Mean (SD)	-2.923 (23.365)	-18.177 (64.821)
SE	3.240	17.978
Median	0.000	-0.800
Min, Max	-128.80, 34.00	-232.80, 18.80

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Table 14.3
Cardiac Biomarkers - Troponin I (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Region: Rest of World

Subgroup Visit	Vutrisiran (HELIOS-A) (N=53)	Patisiran (HELIOS-A) (N=14)
Month 18		
Actual Value		
n	50	12
Mean (SD)	30.078 (52.589)	17.842 (11.214)
SE	7.437	3.237
Median	14.100	12.100
Min, Max	10.00, 366.90	10.00, 45.50
Change from baseline		
n	50	12
Mean (SD)	-3.946 (22.281)	-1.417 (3.718)
SE	3.151	1.073
Median	0.000	0.000
Min, Max	-116.70, 45.50	-11.60, 2.80

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Table 14.3
Cardiac Biomarkers - Troponin I (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Baseline NIS: <50

Subgroup Visit	Vutrisiran (HELIOS-A) (N=78)	Patisiran (HELIOS-A) (N=27)
Baseline		
n	78	27
Mean (SD)	27.535 (59.976)	43.756 (77.856)
SE	6.791	14.983
Median	10.000	14.200
Min, Max	10.00, 483.60	10.00, 325.40
Week 12		
Actual Value		
n	78	26
Mean (SD)	26.195 (72.922)	54.058 (111.836)
SE	8.257	21.933
Median	10.000	10.300
Min, Max	10.00, 647.60	10.00, 443.70
Change from baseline		
n	78	26
Mean (SD)	-1.340 (30.489)	9.731 (42.338)
SE	3.452	8.303
Median	0.000	0.000
Min, Max	-195.60, 164.00	-55.30, 191.10

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Table 14.3
Cardiac Biomarkers - Troponin I (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Baseline NIS: <50

Subgroup Visit	Vutrisiran (HELIOS-A) (N=78)	Patisiran (HELIOS-A) (N=27)
Week 24		
Actual Value		
n	74	25
Mean (SD)	24.893 (68.463)	50.864 (98.630)
SE	7.959	19.726
Median	10.000	10.000
Min, Max	10.00, 591.00	10.00, 398.30
Change from baseline		
n	74	25
Mean (SD)	-2.232 (26.990)	5.164 (30.588)
SE	3.138	6.118
Median	0.000	0.000
Min, Max	-195.60, 107.40	-32.70, 145.70

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Table 14.3
Cardiac Biomarkers - Troponin I (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Baseline NIS: <50

Subgroup Visit	Vutrisiran (HELIOS-A) (N=78)	Patisiran (HELIOS-A) (N=27)
Month 9		
Actual Value		
n	73	25
Mean (SD)	23.773 (63.065)	44.004 (98.880)
SE	7.381	19.776
Median	10.000	10.000
Min, Max	10.00, 541.50	10.00, 481.40
Change from baseline		
n	73	25
Mean (SD)	-3.360 (24.928)	7.716 (32.936)
SE	2.918	6.587
Median	0.000	0.000
Min, Max	-195.60, 57.90	-21.10, 156.00

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Table 14.3
Cardiac Biomarkers - Troponin I (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Baseline NIS: <50

Subgroup Visit	Vutrisiran (HELIOS-A) (N=78)	Patisiran (HELIOS-A) (N=27)
Week 48		
Actual Value		
n	74	27
Mean (SD)	22.522 (47.338)	63.133 (142.636)
SE	5.503	27.450
Median	10.000	10.000
Min, Max	10.00, 400.70	10.00, 605.40
Change from baseline		
n	74	27
Mean (SD)	-5.584 (25.323)	19.378 (67.836)
SE	2.944	13.055
Median	0.000	0.000
Min, Max	-195.60, 12.80	-28.00, 280.00

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Table 14.3
Cardiac Biomarkers - Troponin I (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Baseline NIS: <50

Subgroup Visit	Vutrisiran (HELIOS-A) (N=78)	Patisiran (HELIOS-A) (N=27)
Week 60		
Actual Value		
n	76	24
Mean (SD)	25.945 (59.747)	54.217 (140.698)
SE	6.854	28.720
Median	10.000	10.000
Min, Max	10.00, 499.00	10.00, 635.80
Change from baseline		
n	76	24
Mean (SD)	-1.963 (9.184)	14.675 (66.015)
SE	1.053	13.475
Median	0.000	0.000
Min, Max	-51.90, 15.40	-27.40, 310.40

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Table 14.3
Cardiac Biomarkers - Troponin I (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Baseline NIS: <50

Subgroup Visit	Vutrisiran (HELIOS-A) (N=78)	Patisiran (HELIOS-A) (N=27)
Week 72		
Actual Value		
n	73	23
Mean (SD)	21.795 (42.969)	71.470 (183.783)
SE	5.029	38.321
Median	10.000	10.000
Min, Max	10.00, 354.80	10.00, 665.40
Change from baseline		
n	73	23
Mean (SD)	-3.196 (16.489)	29.430 (106.697)
SE	1.930	22.248
Median	0.000	0.000
Min, Max	-128.80, 20.80	-22.40, 412.80

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Table 14.3
Cardiac Biomarkers - Troponin I (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Baseline NIS: <50

Subgroup Visit	Vutrisiran (HELIOS-A) (N=78)	Patisiran (HELIOS-A) (N=27)
Month 18		
Actual Value		
n	73	25
Mean (SD)	20.852 (43.613)	74.692 (207.647)
SE	5.105	41.529
Median	10.000	10.000
Min, Max	10.00, 366.90	10.00, 871.30
Change from baseline		
n	73	25
Mean (SD)	-6.644 (27.632)	34.564 (137.242)
SE	3.234	27.448
Median	0.000	0.000
Min, Max	-195.60, 32.80	-22.80, 618.70

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Table 14.3
Cardiac Biomarkers - Troponin I (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Baseline NIS: ≥50

Subgroup Visit	Vutrisiran (HELIOS-A) (N=44)	Patisiran (HELIOS-A) (N=15)
Baseline		
n	44	15
Mean (SD)	52.930 (186.574)	111.500 (319.000)
SE	28.127	82.365
Median	15.250	25.800
Min, Max	10.00, 1250.50	10.00, 1262.00
Week 12		
Actual Value		
n	41	14
Mean (SD)	21.498 (17.128)	175.143 (544.721)
SE	2.675	145.583
Median	14.800	28.050
Min, Max	10.00, 79.80	10.00, 2066.80
Change from baseline		
n	41	14
Mean (SD)	-3.144 (13.120)	56.443 (215.559)
SE	2.049	57.611
Median	0.000	1.050
Min, Max	-76.60, 8.90	-28.20, 804.80

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Table 14.3
Cardiac Biomarkers - Troponin I (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Baseline NIS: ≥50

Subgroup Visit	Vutrisiran (HELIOS-A) (N=44)	Patisiran (HELIOS-A) (N=15)
Week 24		
Actual Value		
n	40	11
Mean (SD)	22.530 (19.476)	161.127 (471.168)
SE	3.079	142.062
Median	13.050	18.700
Min, Max	10.00, 81.40	10.00, 1581.30
Change from baseline		
n	40	11
Mean (SD)	-1.523 (15.263)	27.109 (97.009)
SE	2.413	29.249
Median	0.000	0.000
Min, Max	-75.00, 23.90	-9.10, 319.30

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Table 14.3
Cardiac Biomarkers - Troponin I (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Baseline NIS: ≥50

Subgroup Visit	Vutrisiran (HELIOS-A) (N=44)	Patisiran (HELIOS-A) (N=15)
Month 9		
Actual Value		
n	39	13
Mean (SD)	24.854 (23.682)	192.623 (598.561)
SE	3.792	166.011
Median	14.300	28.300
Min, Max	10.00, 113.20	10.00, 2183.70
Change from baseline		
n	39	13
Mean (SD)	-0.249 (13.658)	71.554 (255.758)
SE	2.187	70.935
Median	0.000	0.000
Min, Max	-43.20, 29.30	-17.60, 921.70

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

Alnylam Pharmaceuticals Inc.
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Table 14.3
Cardiac Biomarkers - Troponin I (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Baseline NIS: ≥50

Subgroup Visit	Vutrisiran (HELIOS-A) (N=44)	Patisiran (HELIOS-A) (N=15)
Week 48		
Actual Value		
n	40	12
Mean (SD)	23.370 (20.686)	105.083 (273.735)
SE	3.271	79.020
Median	14.950	20.200
Min, Max	10.00, 90.70	10.00, 971.40
Change from baseline		
n	40	12
Mean (SD)	-1.533 (15.226)	-23.483 (85.499)
SE	2.407	24.682
Median	0.000	0.000
Min, Max	-65.70, 34.80	-290.60, 42.20

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

Alnylam Pharmaceuticals Inc.
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Table 14.3
Cardiac Biomarkers - Troponin I (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Baseline NIS: ≥50

Subgroup Visit	Vutrisiran (HELIOS-A) (N=44)	Patisiran (HELIOS-A) (N=15)
Week 60		
Actual Value		
n	42	11
Mean (SD)	22.226 (20.416)	170.673 (481.230)
SE	3.150	145.096
Median	14.350	24.200
Min, Max	10.00, 110.30	10.00, 1620.80
Change from baseline		
n	42	11
Mean (SD)	-2.067 (11.162)	31.327 (109.081)
SE	1.722	32.889
Median	0.000	0.000
Min, Max	-46.10, 17.40	-20.20, 358.80

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

Alnylam Pharmaceuticals Inc.
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Table 14.3
Cardiac Biomarkers - Troponin I (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Baseline NIS: ≥50

Subgroup Visit	Vutrisiran (HELIOS-A) (N=44)	Patisiran (HELIOS-A) (N=15)
Week 72		
Actual Value		
n	41	12
Mean (SD)	24.602 (20.235)	106.825 (290.824)
SE	3.160	83.954
Median	14.500	20.000
Min, Max	10.00, 77.60	10.00, 1029.20
Change from baseline		
n	41	12
Mean (SD)	0.237 (16.125)	-21.742 (67.431)
SE	2.518	19.466
Median	0.000	-1.550
Min, Max	-78.80, 34.00	-232.80, 18.80

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

Alnylam Pharmaceuticals Inc.
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Table 14.3
Cardiac Biomarkers - Troponin I (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Baseline NIS: ≥50

Subgroup Visit	Vutrisiran (HELIOS-A) (N=44)	Patisiran (HELIOS-A) (N=15)
Month 18		
Actual Value		
n	39	11
Mean (SD)	24.279 (21.767)	26.200 (21.744)
SE	3.486	6.556
Median	14.400	18.000
Min, Max	10.00, 93.70	10.00, 83.60
Change from baseline		
n	39	11
Mean (SD)	-0.818 (15.963)	0.673 (13.131)
SE	2.556	3.959
Median	0.000	0.000
Min, Max	-67.60, 45.50	-28.10, 30.00

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

Alnylam Pharmaceuticals Inc.
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Table 14.3
Cardiac Biomarkers - Troponin I (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Previous Tetramer Stabilizer Use: Yes

Subgroup Visit	Vutrisiran (HELIOS-A) (N=75)	Patisiran (HELIOS-A) (N=33)
Baseline		
n	75	33
Mean (SD)	27.405 (61.336)	70.324 (221.007)
SE	7.082	38.472
Median	10.000	17.900
Min, Max	10.00, 483.60	10.00, 1262.00
Week 12		
Actual Value		
n	73	32
Mean (SD)	25.478 (75.005)	99.906 (365.625)
SE	8.779	64.634
Median	10.000	15.950
Min, Max	10.00, 647.60	10.00, 2066.80
Change from baseline		
n	73	32
Mean (SD)	-1.745 (31.821)	28.288 (142.626)
SE	3.724	25.213
Median	0.000	0.000
Min, Max	-195.60, 164.00	-28.20, 804.80

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

Alnylam Pharmaceuticals Inc.
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Table 14.3
Cardiac Biomarkers - Troponin I (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Previous Tetramer Stabilizer Use: Yes

Subgroup Visit	Vutrisiran (HELIOS-A) (N=75)	Patisiran (HELIOS-A) (N=33)
Week 24		
Actual Value		
n	72	29
Mean (SD)	25.197 (69.410)	83.441 (294.138)
SE	8.180	54.620
Median	10.000	10.500
Min, Max	10.00, 591.00	10.00, 1581.30
Change from baseline		
n	72	29
Mean (SD)	-2.228 (28.725)	10.883 (59.554)
SE	3.385	11.059
Median	0.000	0.000
Min, Max	-195.60, 107.40	-11.40, 319.30

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Alnylam Pharmaceuticals Inc.
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Table 14.3
Cardiac Biomarkers - Troponin I (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Previous Tetramer Stabilizer Use: Yes

Subgroup Visit	Vutrisiran (HELIOS-A) (N=75)	Patisiran (HELIOS-A) (N=33)
Month 9		
Actual Value		
n	74	32
Mean (SD)	23.485 (62.919)	103.975 (388.526)
SE	7.314	68.682
Median	10.000	13.200
Min, Max	10.00, 541.50	10.00, 2183.70
Change from baseline		
n	74	32
Mean (SD)	-3.505 (25.292)	34.200 (164.693)
SE	2.940	29.114
Median	0.000	0.000
Min, Max	-195.60, 57.90	-21.10, 921.70

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

Alnylam Pharmaceuticals Inc.
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Table 14.3
Cardiac Biomarkers - Troponin I (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Previous Tetramer Stabilizer Use: Yes

Subgroup Visit	Vutrisiran (HELIOS-A) (N=75)	Patisiran (HELIOS-A) (N=33)
Week 48		
Actual Value		
n	71	31
Mean (SD)	21.246 (47.632)	69.490 (198.414)
SE	5.653	35.636
Median	10.000	10.000
Min, Max	10.00, 400.70	10.00, 971.40
Change from baseline		
n	71	31
Mean (SD)	-6.104 (26.359)	-1.532 (74.631)
SE	3.128	13.404
Median	0.000	0.000
Min, Max	-195.60, 7.60	-290.60, 280.00

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Table 14.3
Cardiac Biomarkers - Troponin I (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Previous Tetramer Stabilizer Use: Yes

Subgroup Visit	Vutrisiran (HELIOS-A) (N=75)	Patisiran (HELIOS-A) (N=33)
Week 60		
Actual Value		
n	73	29
Mean (SD)	25.699 (60.705)	95.055 (315.265)
SE	7.105	58.543
Median	10.000	11.900
Min, Max	10.00, 499.00	10.00, 1620.80
Change from baseline		
n	73	29
Mean (SD)	-1.525 (10.221)	20.948 (87.597)
SE	1.196	16.266
Median	0.000	0.000
Min, Max	-51.90, 15.40	-27.40, 358.80

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

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Table 14.3
Cardiac Biomarkers - Troponin I (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Previous Tetramer Stabilizer Use: Yes

Subgroup Visit	Vutrisiran (HELIOS-A) (N=75)	Patisiran (HELIOS-A) (N=33)
Week 72		
Actual Value		
n	71	29
Mean (SD)	20.779 (42.164)	74.914 (217.150)
SE	5.004	40.324
Median	10.000	14.900
Min, Max	10.00, 354.80	10.00, 1029.20
Change from baseline		
n	71	29
Mean (SD)	-3.293 (19.036)	0.245 (74.515)
SE	2.259	13.837
Median	0.000	0.000
Min, Max	-128.80, 20.80	-232.80, 314.70

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

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Table 14.3
Cardiac Biomarkers - Troponin I (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Previous Tetramer Stabilizer Use: Yes

Subgroup Visit	Vutrisiran (HELIOS-A) (N=75)	Patisiran (HELIOS-A) (N=33)
Month 18		
Actual Value		
n	69	29
Mean (SD)	20.586 (44.401)	41.152 (115.965)
SE	5.345	21.534
Median	10.000	10.800
Min, Max	10.00, 366.90	10.00, 638.40
Change from baseline		
n	69	29
Mean (SD)	-6.255 (29.223)	9.093 (59.255)
SE	3.518	11.003
Median	0.000	0.000
Min, Max	-195.60, 32.80	-28.10, 313.00

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

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Table 14.3
Cardiac Biomarkers - Troponin I (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Previous Tetramer Stabilizer Use: No

Subgroup Visit	Vutrisiran (HELIOS-A) (N=47)	Patisiran (HELIOS-A) (N=9)
Baseline		
n	47	9
Mean (SD)	51.515 (180.384)	59.244 (88.482)
SE	26.312	29.494
Median	14.800	16.000
Min, Max	10.00, 1250.50	10.00, 252.60
Week 12		
Actual Value		
n	46	8
Mean (SD)	23.146 (19.193)	82.563 (149.966)
SE	2.830	53.021
Median	10.950	16.350
Min, Max	10.00, 79.10	10.00, 443.70
Change from baseline		
n	46	8
Mean (SD)	-2.304 (11.187)	17.250 (73.030)
SE	1.649	25.820
Median	0.000	0.400
Min, Max	-39.50, 23.10	-55.30, 191.10

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Table 14.3
Cardiac Biomarkers - Troponin I (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Previous Tetramer Stabilizer Use: No

Subgroup Visit	Vutrisiran (HELIOS-A) (N=47)	Patisiran (HELIOS-A) (N=9)
Week 24		
Actual Value		
n	42	7
Mean (SD)	22.121 (18.992)	89.171 (143.564)
SE	2.931	54.262
Median	10.900	15.700
Min, Max	10.00, 78.50	10.00, 398.30
Change from baseline		
n	42	7
Mean (SD)	-1.564 (9.475)	15.957 (58.863)
SE	1.462	22.248
Median	0.000	0.000
Min, Max	-44.00, 20.00	-32.70, 145.70

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Table 14.3
Cardiac Biomarkers - Troponin I (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Previous Tetramer Stabilizer Use: No

Subgroup Visit	Vutrisiran (HELIOS-A) (N=47)	Patisiran (HELIOS-A) (N=9)
Month 9		
Actual Value		
n	38	6
Mean (SD)	25.442 (22.425)	46.167 (72.741)
SE	3.638	29.696
Median	13.000	12.950
Min, Max	10.00, 82.70	10.00, 193.00
Change from baseline		
n	38	6
Mean (SD)	0.116 (11.683)	4.783 (11.147)
SE	1.895	4.551
Median	0.000	2.500
Min, Max	-25.00, 29.30	-5.10, 24.80

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Table 14.3
Cardiac Biomarkers - Troponin I (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Previous Tetramer Stabilizer Use: No

Subgroup Visit	Vutrisiran (HELIOS-A) (N=47)	Patisiran (HELIOS-A) (N=9)
Week 48		
Actual Value		
n	43	8
Mean (SD)	25.416 (22.366)	101.425 (160.491)
SE	3.411	56.742
Median	12.100	14.350
Min, Max	10.00, 80.20	10.00, 363.80
Change from baseline		
n	43	8
Mean (SD)	-0.956 (12.849)	36.113 (74.845)
SE	1.959	26.462
Median	0.000	0.350
Min, Max	-34.60, 34.80	-11.60, 195.60

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

Alnylam Pharmaceuticals Inc.
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Table 14.3
Cardiac Biomarkers - Troponin I (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Previous Tetramer Stabilizer Use: No

Subgroup Visit	Vutrisiran (HELIOS-A) (N=47)	Patisiran (HELIOS-A) (N=9)
Week 60		
Actual Value		
n	45	6
Mean (SD)	22.873 (21.129)	70.333 (132.211)
SE	3.150	53.975
Median	10.800	12.400
Min, Max	10.00, 99.60	10.00, 339.30
Change from baseline		
n	45	6
Mean (SD)	-2.771 (9.377)	14.883 (35.436)
SE	1.398	14.466
Median	0.000	0.000
Min, Max	-39.50, 17.40	-4.50, 86.70

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

Alnylam Pharmaceuticals Inc.
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Table 14.3
Cardiac Biomarkers - Troponin I (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Previous Tetramer Stabilizer Use: No

Subgroup Visit	Vutrisiran (HELIOS-A) (N=47)	Patisiran (HELIOS-A) (N=9)
Week 72		
Actual Value		
n	43	6
Mean (SD)	26.149 (24.054)	125.533 (264.668)
SE	3.668	108.050
Median	10.100	15.450
Min, Max	10.00, 96.30	10.00, 665.40
Change from baseline		
n	43	6
Mean (SD)	0.237 (10.451)	68.150 (168.953)
SE	1.594	68.975
Median	0.000	0.250
Min, Max	-27.40, 34.00	-11.60, 412.80

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

Alnylam Pharmaceuticals Inc.
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Table 14.3
Cardiac Biomarkers - Troponin I (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Previous Tetramer Stabilizer Use: No

Subgroup Visit	Vutrisiran (HELIOS-A) (N=47)	Patisiran (HELIOS-A) (N=9)
Month 18		
Actual Value		
n	43	7
Mean (SD)	24.388 (22.261)	137.443 (323.698)
SE	3.395	122.346
Median	13.800	14.200
Min, Max	10.00, 93.70	10.00, 871.30
Change from baseline		
n	43	7
Mean (SD)	-1.984 (12.878)	86.829 (234.578)
SE	1.964	88.662
Median	0.000	0.000
Min, Max	-34.30, 45.50	-11.60, 618.70

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

Alnylam Pharmaceuticals Inc.
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Table 14.3
Cardiac Biomarkers - Troponin I (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Genotype: V30M

Subgroup Visit	Vutrisiran (HELIOS-A) (N=54)	Patisiran (HELIOS-A) (N=20)
Baseline		
n	54	20
Mean (SD)	17.094 (27.398)	21.700 (15.856)
SE	3.728	3.545
Median	10.000	11.950
Min, Max	10.00, 205.60	10.00, 54.70
Week 12		
Actual Value		
n	52	19
Mean (SD)	12.952 (7.220)	23.100 (22.225)
SE	1.001	5.099
Median	10.000	13.400
Min, Max	10.00, 45.60	10.00, 90.90
Change from baseline		
n	52	19
Mean (SD)	-3.490 (27.598)	1.779 (9.484)
SE	3.827	2.176
Median	0.000	0.000
Min, Max	-195.60, 23.10	-8.90, 36.20

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

Alnylam Pharmaceuticals Inc.
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Table 14.3
Cardiac Biomarkers - Troponin I (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Genotype: V30M

Subgroup Visit	Vutrisiran (HELIOS-A) (N=54)	Patisiran (HELIOS-A) (N=20)
Week 24		
Actual Value		
n	52	16
Mean (SD)	12.737 (8.337)	17.525 (15.749)
SE	1.156	3.937
Median	10.000	10.000
Min, Max	10.00, 60.70	10.00, 58.30
Change from baseline		
n	52	16
Mean (SD)	-3.706 (27.607)	-0.938 (6.040)
SE	3.828	1.510
Median	0.000	0.000
Min, Max	-195.60, 23.60	-11.60, 15.70

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

Alnylam Pharmaceuticals Inc.
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Table 14.3
Cardiac Biomarkers - Troponin I (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Genotype: V30M

Subgroup Visit	Vutrisiran (HELIOS-A) (N=54)	Patisiran (HELIOS-A) (N=20)
Month 9		
Actual Value		
n	50	19
Mean (SD)	11.974 (4.621)	21.121 (18.494)
SE	0.654	4.243
Median	10.000	10.000
Min, Max	10.00, 35.30	10.00, 79.30
Change from baseline		
n	50	19
Mean (SD)	-4.556 (28.122)	-0.584 (12.729)
SE	3.977	2.920
Median	0.000	0.000
Min, Max	-195.60, 13.90	-21.10, 36.70

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

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Table 14.3
Cardiac Biomarkers - Troponin I (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Genotype: V30M

Subgroup Visit	Vutrisiran (HELIOS-A) (N=54)	Patisiran (HELIOS-A) (N=20)
Week 48		
Actual Value		
n	50	20
Mean (SD)	12.394 (5.061)	17.580 (14.241)
SE	0.716	3.184
Median	10.000	10.000
Min, Max	10.00, 28.40	10.00, 62.70
Change from baseline		
n	50	20
Mean (SD)	-4.222 (27.971)	-4.120 (10.727)
SE	3.956	2.399
Median	0.000	0.000
Min, Max	-195.60, 12.80	-28.00, 20.10

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Alnylam Pharmaceuticals Inc.
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Table 14.3
Cardiac Biomarkers - Troponin I (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Genotype: V30M

Subgroup Visit	Vutrisiran (HELIOS-A) (N=54)	Patisiran (HELIOS-A) (N=20)
Week 60		
Actual Value		
n	53	17
Mean (SD)	15.509 (20.646)	15.459 (8.793)
SE	2.836	2.133
Median	10.000	10.000
Min, Max	10.00, 153.70	10.00, 41.30
Change from baseline		
n	53	17
Mean (SD)	-0.811 (8.295)	-5.706 (9.112)
SE	1.139	2.210
Median	0.000	0.000
Min, Max	-51.90, 14.20	-27.40, 1.30

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Alnylam Pharmaceuticals Inc.
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Table 14.3
Cardiac Biomarkers - Troponin I (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Genotype: V30M

Subgroup Visit	Vutrisiran (HELIOS-A) (N=54)	Patisiran (HELIOS-A) (N=20)
Week 72		
Actual Value		
n	51	19
Mean (SD)	13.004 (6.974)	17.226 (11.224)
SE	0.977	2.575
Median	10.000	11.200
Min, Max	10.00, 48.20	10.00, 45.10
Change from baseline		
n	51	19
Mean (SD)	0.437 (4.514)	-5.089 (9.134)
SE	0.632	2.096
Median	0.000	0.000
Min, Max	-19.60, 14.60	-25.10, 4.90

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Alnylam Pharmaceuticals Inc.
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Table 14.3
Cardiac Biomarkers - Troponin I (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Genotype: V30M

Subgroup Visit	Vutrisiran (HELIOS-A) (N=54)	Patisiran (HELIOS-A) (N=20)
Month 18		
Actual Value		
n	51	19
Mean (SD)	12.125 (5.558)	19.274 (18.056)
SE	0.778	4.142
Median	10.000	10.000
Min, Max	10.00, 43.80	10.00, 83.60
Change from baseline		
n	51	19
Mean (SD)	-4.353 (27.555)	-3.042 (12.166)
SE	3.858	2.791
Median	0.000	0.000
Min, Max	-195.60, 6.70	-28.10, 30.00

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

Alnylam Pharmaceuticals Inc.
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Table 14.3
Cardiac Biomarkers - Troponin I (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Genotype: non-V30M

Subgroup Visit	Vutrisiran (HELIOS-A) (N=68)	Patisiran (HELIOS-A) (N=22)
Baseline		
n	68	22
Mean (SD)	52.257 (159.988)	109.995 (270.806)
SE	19.401	57.736
Median	15.400	24.500
Min, Max	10.00, 1250.50	10.00, 1262.00
Week 12		
Actual Value		
n	67	21
Mean (SD)	33.599 (78.494)	162.790 (452.766)
SE	9.590	98.802
Median	16.800	27.200
Min, Max	10.00, 647.60	10.00, 2066.80
Change from baseline		
n	67	21
Mean (SD)	-0.775 (24.461)	48.067 (179.685)
SE	2.988	39.210
Median	0.000	0.000
Min, Max	-76.60, 164.00	-55.30, 804.80

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

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Table 14.3
Cardiac Biomarkers - Troponin I (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Genotype: non-V30M

Subgroup Visit	Vutrisiran (HELIOS-A) (N=68)	Patisiran (HELIOS-A) (N=22)
Week 24		
Actual Value		
n	62	20
Mean (SD)	33.565 (74.799)	138.180 (356.386)
SE	9.500	79.690
Median	15.900	20.650
Min, Max	10.00, 591.00	10.00, 1581.30
Change from baseline		
n	62	20
Mean (SD)	-0.539 (19.470)	22.115 (77.789)
SE	2.473	17.394
Median	0.000	0.000
Min, Max	-75.00, 107.40	-32.70, 319.30

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

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Table 14.3
Cardiac Biomarkers - Troponin I (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Genotype: non-V30M

Subgroup Visit	Vutrisiran (HELIOS-A) (N=68)	Patisiran (HELIOS-A) (N=22)
Month 9		
Actual Value		
n	62	19
Mean (SD)	33.968 (69.337)	168.574 (500.564)
SE	8.806	114.837
Median	14.900	20.400
Min, Max	10.00, 541.50	10.00, 2183.70
Change from baseline		
n	62	19
Mean (SD)	-0.439 (14.517)	59.695 (211.922)
SE	1.844	48.618
Median	0.000	0.000
Min, Max	-43.20, 57.90	-7.10, 921.70

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

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Table 14.3
Cardiac Biomarkers - Troponin I (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Genotype: non-V30M

Subgroup Visit	Vutrisiran (HELIOS-A) (N=68)	Patisiran (HELIOS-A) (N=22)
Week 48		
Actual Value		
n	64	19
Mean (SD)	30.964 (51.848)	137.579 (260.732)
SE	6.481	59.816
Median	14.050	18.400
Min, Max	10.00, 400.70	10.00, 971.40
Change from baseline		
n	64	19
Mean (SD)	-4.116 (16.876)	17.042 (107.695)
SE	2.110	24.707
Median	0.000	0.000
Min, Max	-82.90, 34.80	-290.60, 280.00

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

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Table 14.3
Cardiac Biomarkers - Troponin I (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Genotype: non-V30M

Subgroup Visit	Vutrisiran (HELIOS-A) (N=68)	Patisiran (HELIOS-A) (N=22)
Week 60		
Actual Value		
n	65	18
Mean (SD)	32.051 (63.127)	161.989 (397.378)
SE	7.830	93.663
Median	13.700	19.500
Min, Max	10.00, 499.00	10.00, 1620.80
Change from baseline		
n	65	18
Mean (SD)	-2.969 (10.983)	44.100 (108.001)
SE	1.362	25.456
Median	0.000	0.000
Min, Max	-46.10, 17.40	-4.50, 358.80

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

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Table 14.3
Cardiac Biomarkers - Troponin I (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Genotype: non-V30M

Subgroup Visit	Vutrisiran (HELIOS-A) (N=68)	Patisiran (HELIOS-A) (N=22)
Week 72		
Actual Value		
n	63	16
Mean (SD)	30.738 (47.217)	162.400 (316.014)
SE	5.949	79.004
Median	11.900	19.450
Min, Max	10.00, 354.80	10.00, 1029.20
Change from baseline		
n	63	16
Mean (SD)	-3.903 (21.529)	32.044 (143.211)
SE	2.712	35.803
Median	0.000	0.000
Min, Max	-128.80, 34.00	-232.80, 412.80

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

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Table 14.3
Cardiac Biomarkers - Troponin I (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Genotype: non-V30M

Subgroup Visit	Vutrisiran (HELIOS-A) (N=68)	Patisiran (HELIOS-A) (N=22)
Month 18		
Actual Value		
n	61	17
Mean (SD)	30.339 (49.074)	105.253 (248.157)
SE	6.283	60.187
Median	13.600	14.200
Min, Max	10.00, 366.90	10.00, 871.30
Change from baseline		
n	61	17
Mean (SD)	-4.834 (21.428)	54.665 (163.937)
SE	2.744	39.761
Median	0.000	0.000
Min, Max	-116.70, 45.50	-4.20, 618.70

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

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Table 14.3
Cardiac Biomarkers - Troponin I (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

FAP Stage: I

Subgroup Visit	Vutrisiran (HELIOS-A) (N=84)	Patisiran (HELIOS-A) (N=31)
Baseline		
n	84	31
Mean (SD)	24.105 (56.328)	68.068 (228.616)
SE	6.146	41.061
Median	10.000	14.200
Min, Max	10.00, 483.60	10.00, 1262.00
Week 12		
Actual Value		
n	84	29
Mean (SD)	23.995 (70.100)	103.221 (384.680)
SE	7.649	71.433
Median	10.000	10.600
Min, Max	10.00, 647.60	10.00, 2066.80
Change from baseline		
n	84	29
Mean (SD)	-0.110 (28.580)	31.824 (149.527)
SE	3.118	27.767
Median	0.000	0.000
Min, Max	-195.60, 164.00	-8.90, 804.80

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Table 14.3
Cardiac Biomarkers - Troponin I (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

FAP Stage: I

Subgroup Visit	Vutrisiran (HELIOS-A) (N=84)	Patisiran (HELIOS-A) (N=31)
Week 24		
Actual Value		
n	80	28
Mean (SD)	22.540 (65.401)	85.014 (299.402)
SE	7.312	56.582
Median	10.000	10.100
Min, Max	10.00, 591.00	10.00, 1581.30
Change from baseline		
n	80	28
Mean (SD)	-1.759 (25.744)	11.425 (60.630)
SE	2.878	11.458
Median	0.000	0.000
Min, Max	-195.60, 107.40	-11.60, 319.30

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Table 14.3
Cardiac Biomarkers - Troponin I (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

FAP Stage: I

Subgroup Visit	Vutrisiran (HELIOS-A) (N=84)	Patisiran (HELIOS-A) (N=31)
Month 9		
Actual Value		
n	79	29
Mean (SD)	22.605 (60.742)	109.293 (408.386)
SE	6.834	75.835
Median	10.000	10.900
Min, Max	10.00, 541.50	10.00, 2183.70
Change from baseline		
n	79	29
Mean (SD)	-2.200 (24.356)	37.645 (172.734)
SE	2.740	32.076
Median	0.000	0.000
Min, Max	-195.60, 57.90	-21.10, 921.70

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Table 14.3
Cardiac Biomarkers - Troponin I (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

FAP Stage: I

Subgroup Visit	Vutrisiran (HELIOS-A) (N=84)	Patisiran (HELIOS-A) (N=31)
Week 48		
Actual Value		
n	79	30
Mean (SD)	20.333 (45.203)	67.793 (202.011)
SE	5.086	36.882
Median	10.000	10.000
Min, Max	10.00, 400.70	10.00, 971.40
Change from baseline		
n	79	30
Mean (SD)	-4.311 (24.479)	-2.187 (75.367)
SE	2.754	13.760
Median	0.000	0.000
Min, Max	-195.60, 27.70	-290.60, 280.00

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

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Table 14.3
Cardiac Biomarkers - Troponin I (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

FAP Stage: I

Subgroup Visit	Vutrisiran (HELIOS-A) (N=84)	Patisiran (HELIOS-A) (N=31)
Week 60		
Actual Value		
n	82	27
Mean (SD)	22.716 (56.426)	98.085 (326.971)
SE	6.231	62.926
Median	10.000	10.000
Min, Max	10.00, 499.00	10.00, 1620.80
Change from baseline		
n	82	27
Mean (SD)	-1.651 (8.330)	23.078 (90.369)
SE	0.920	17.391
Median	0.000	0.000
Min, Max	-51.90, 15.40	-27.40, 358.80

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

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Table 14.3
Cardiac Biomarkers - Troponin I (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

FAP Stage: I

Subgroup Visit	Vutrisiran (HELIOS-A) (N=84)	Patisiran (HELIOS-A) (N=31)
Week 72		
Actual Value		
n	80	27
Mean (SD)	19.378 (39.802)	76.930 (225.200)
SE	4.450	43.340
Median	10.000	10.000
Min, Max	10.00, 354.80	10.00, 1029.20
Change from baseline		
n	80	27
Mean (SD)	-2.798 (15.855)	0.889 (77.002)
SE	1.773	14.819
Median	0.000	0.000
Min, Max	-128.80, 20.80	-232.80, 314.70

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Table 14.3
Cardiac Biomarkers - Troponin I (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

FAP Stage: I

Subgroup Visit	Vutrisiran (HELIOS-A) (N=84)	Patisiran (HELIOS-A) (N=31)
Month 18		
Actual Value		
n	79	28
Mean (SD)	19.299 (41.691)	38.439 (117.946)
SE	4.691	22.290
Median	10.000	10.000
Min, Max	10.00, 366.90	10.00, 638.40
Change from baseline		
n	79	28
Mean (SD)	-5.287 (26.941)	8.889 (59.917)
SE	3.031	11.323
Median	0.000	0.000
Min, Max	-195.60, 45.50	-22.80, 313.00

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Table 14.3
Cardiac Biomarkers - Troponin I (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

FAP Stage: II&III

Subgroup Visit	Vutrisiran (HELIOS-A) (N=38)	Patisiran (HELIOS-A) (N=11)
Baseline		
n	38	11
Mean (SD)	64.521 (200.396)	67.618 (76.514)
SE	32.508	23.070
Median	19.900	44.600
Min, Max	10.00, 1250.50	10.00, 252.60
Week 12		
Actual Value		
n	35	11
Mean (SD)	25.971 (20.168)	78.555 (124.588)
SE	3.409	37.565
Median	19.800	38.400
Min, Max	10.00, 79.80	10.00, 443.70
Change from baseline		
n	35	11
Mean (SD)	-6.406 (16.956)	10.936 (62.616)
SE	2.866	18.879
Median	0.000	1.500
Min, Max	-76.60, 8.90	-55.30, 191.10

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

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Table 14.3
Cardiac Biomarkers - Troponin I (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

FAP Stage: II&III

Subgroup Visit	Vutrisiran (HELIOS-A) (N=38)	Patisiran (HELIOS-A) (N=11)
Week 24		
Actual Value		
n	34	8
Mean (SD)	27.650 (23.726)	82.950 (134.156)
SE	4.069	47.431
Median	16.800	23.150
Min, Max	10.00, 86.10	10.00, 398.30
Change from baseline		
n	34	8
Mean (SD)	-2.512 (17.327)	13.425 (54.728)
SE	2.972	19.349
Median	0.000	-0.950
Min, Max	-75.00, 23.90	-32.70, 145.70

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Table 14.3
Cardiac Biomarkers - Troponin I (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

FAP Stage: II&III

Subgroup Visit	Vutrisiran (HELIOS-A) (N=38)	Patisiran (HELIOS-A) (N=11)
Month 9		
Actual Value		
n	33	9
Mean (SD)	27.845 (24.536)	48.300 (58.640)
SE	4.271	19.547
Median	15.900	28.500
Min, Max	10.00, 113.20	10.00, 193.00
Change from baseline		
n	33	9
Mean (SD)	-2.461 (13.470)	3.489 (17.282)
SE	2.345	5.761
Median	0.000	0.000
Min, Max	-43.20, 27.90	-17.60, 37.40

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Table 14.3
Cardiac Biomarkers - Troponin I (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

FAP Stage: II&III

Subgroup Visit	Vutrisiran (HELIOS-A) (N=38)	Patisiran (HELIOS-A) (N=11)
Week 48		
Actual Value		
n	35	9
Mean (SD)	28.431 (23.839)	103.533 (148.128)
SE	4.029	49.376
Median	17.400	22.000
Min, Max	10.00, 90.70	10.00, 363.80
Change from baseline		
n	35	9
Mean (SD)	-3.826 (16.746)	34.111 (71.999)
SE	2.831	24.000
Median	0.000	0.000
Min, Max	-65.70, 34.80	-24.10, 195.60

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Table 14.3
Cardiac Biomarkers - Troponin I (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

FAP Stage: II&III

Subgroup Visit	Vutrisiran (HELIOS-A) (N=38)	Patisiran (HELIOS-A) (N=11)
Week 60		
Actual Value		
n	36	8
Mean (SD)	28.961 (27.422)	66.288 (111.812)
SE	4.570	39.531
Median	16.350	25.050
Min, Max	10.00, 110.30	10.00, 339.30
Change from baseline		
n	36	8
Mean (SD)	-2.794 (12.852)	9.213 (33.367)
SE	2.142	11.797
Median	0.000	0.000
Min, Max	-46.10, 17.40	-20.20, 86.70

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Table 14.3
Cardiac Biomarkers - Troponin I (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

FAP Stage: II&III

Subgroup Visit	Vutrisiran (HELIOS-A) (N=38)	Patisiran (HELIOS-A) (N=11)
Week 72		
Actual Value		
n	34	8
Mean (SD)	30.868 (25.359)	106.075 (226.609)
SE	4.349	80.118
Median	21.050	22.900
Min, Max	10.00, 96.30	10.00, 665.40
Change from baseline		
n	34	8
Mean (SD)	0.006 (17.616)	49.000 (147.683)
SE	3.021	52.214
Median	0.000	1.500
Min, Max	-78.80, 34.00	-25.10, 412.80

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

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Table 14.3
Cardiac Biomarkers - Troponin I (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

FAP Stage: II&III

Subgroup Visit	Vutrisiran (HELIOS-A) (N=38)	Patisiran (HELIOS-A) (N=11)
Month 18		
Actual Value		
n	33	8
Mean (SD)	28.621 (23.489)	134.900 (298.570)
SE	4.089	105.560
Median	19.700	20.500
Min, Max	10.00, 88.90	10.00, 871.30
Change from baseline		
n	33	8
Mean (SD)	-3.006 (16.571)	77.825 (219.105)
SE	2.885	77.465
Median	0.000	0.450
Min, Max	-67.60, 23.20	-28.10, 618.70

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Table 14.3
Cardiac Biomarkers - Troponin I (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Cardiac Subpopulation: Yes

Subgroup Visit	Vutrisiran (HELIOS-A) (N=40)	Patisiran (HELIOS-A) (N=14)
Baseline		
n	40	14
Mean (SD)	68.740 (206.550)	150.836 (334.228)
SE	32.658	89.326
Median	16.800	28.350
Min, Max	10.00, 1250.50	10.00, 1262.00
Week 12		
Actual Value		
n	38	13
Mean (SD)	41.100 (102.543)	243.031 (567.958)
SE	16.635	157.523
Median	18.800	28.900
Min, Max	10.00, 647.60	10.00, 2066.80
Change from baseline		
n	38	13
Mean (SD)	1.913 (31.482)	82.815 (223.835)
SE	5.107	62.081
Median	0.150	1.500
Min, Max	-76.60, 164.00	-7.70, 804.80

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

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Table 14.3
Cardiac Biomarkers - Troponin I (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Cardiac Subpopulation: Yes

Subgroup Visit	Vutrisiran (HELIOS-A) (N=40)	Patisiran (HELIOS-A) (N=14)
Week 24		
Actual Value		
n	37	12
Mean (SD)	40.678 (95.150)	208.375 (452.521)
SE	15.643	130.631
Median	16.500	23.150
Min, Max	10.00, 591.00	10.00, 1581.30
Change from baseline		
n	37	12
Mean (SD)	1.735 (23.561)	38.650 (97.987)
SE	3.873	28.286
Median	0.000	0.000
Min, Max	-75.00, 107.40	-9.10, 319.30

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

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Table 14.3
Cardiac Biomarkers - Troponin I (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Cardiac Subpopulation: Yes

Subgroup Visit	Vutrisiran (HELIOS-A) (N=40)	Patisiran (HELIOS-A) (N=14)
Month 9		
Actual Value		
n	37	13
Mean (SD)	42.181 (87.969)	228.123 (601.148)
SE	14.462	166.728
Median	15.900	28.300
Min, Max	10.00, 541.50	10.00, 2183.70
Change from baseline		
n	37	13
Mean (SD)	2.616 (16.645)	85.115 (255.241)
SE	2.736	70.791
Median	0.000	0.000
Min, Max	-43.20, 57.90	-17.60, 921.70

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Table 14.3
Cardiac Biomarkers - Troponin I (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Cardiac Subpopulation: Yes

Subgroup Visit	Vutrisiran (HELIOS-A) (N=40)	Patisiran (HELIOS-A) (N=14)
Week 48		
Actual Value		
n	38	13
Mean (SD)	35.929 (64.565)	167.492 (300.667)
SE	10.474	83.390
Median	15.200	20.600
Min, Max	10.00, 400.70	10.00, 971.40
Change from baseline		
n	38	13
Mean (SD)	-3.082 (20.655)	7.446 (121.086)
SE	3.351	33.583
Median	0.000	0.000
Min, Max	-82.90, 34.80	-290.60, 280.00

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

Alnylam Pharmaceuticals Inc.
ALN-TTRSC02-002

Table 14.3
Cardiac Biomarkers - Troponin I (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Cardiac Subpopulation: Yes

Subgroup Visit	Vutrisiran (HELIOS-A) (N=40)	Patisiran (HELIOS-A) (N=14)
Week 60		
Actual Value		
n	38	12
Mean (SD)	36.853 (80.015)	235.925 (475.491)
SE	12.980	137.262
Median	16.000	30.300
Min, Max	10.00, 499.00	10.00, 1620.80
Change from baseline		
n	38	12
Mean (SD)	-2.158 (11.712)	63.375 (129.861)
SE	1.900	37.488
Median	0.000	3.450
Min, Max	-46.10, 17.40	-20.20, 358.80

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

Alnylam Pharmaceuticals Inc.
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Table 14.3
Cardiac Biomarkers - Troponin I (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Cardiac Subpopulation: Yes

Subgroup Visit	Vutrisiran (HELIOS-A) (N=40)	Patisiran (HELIOS-A) (N=14)
Week 72		
Actual Value		
n	37	13
Mean (SD)	35.319 (58.203)	196.085 (343.853)
SE	9.569	95.368
Median	15.600	22.400
Min, Max	10.00, 354.80	10.00, 1029.20
Change from baseline		
n	37	13
Mean (SD)	-4.246 (26.775)	36.038 (160.180)
SE	4.402	44.426
Median	0.000	-0.800
Min, Max	-128.80, 34.00	-232.80, 412.80

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

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Table 14.3
Cardiac Biomarkers - Troponin I (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Cardiac Subpopulation: Yes

Subgroup Visit	Vutrisiran (HELIOS-A) (N=40)	Patisiran (HELIOS-A) (N=14)
Month 18		
Actual Value		
n	37	11
Mean (SD)	34.135 (60.374)	154.582 (301.495)
SE	9.925	90.904
Median	15.800	23.000
Min, Max	10.00, 366.90	10.00, 871.30
Change from baseline		
n	37	11
Mean (SD)	-5.473 (25.314)	81.073 (202.331)
SE	4.162	61.005
Median	-0.100	0.000
Min, Max	-116.70, 45.50	-28.10, 618.70

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

Alnylam Pharmaceuticals Inc.
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Table 14.3
Cardiac Biomarkers - Troponin I (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Cardiac Subpopulation: No

Subgroup Visit	Vutrisiran (HELIOS-A) (N=82)	Patisiran (HELIOS-A) (N=28)
Baseline		
n	82	28
Mean (SD)	21.061 (28.756)	26.507 (33.348)
SE	3.176	6.302
Median	10.000	12.300
Min, Max	10.00, 205.60	10.00, 168.20
Week 12		
Actual Value		
n	81	27
Mean (SD)	16.825 (14.784)	25.856 (26.805)
SE	1.643	5.159
Median	10.000	13.900
Min, Max	10.00, 79.10	10.00, 112.90
Change from baseline		
n	81	27
Mean (SD)	-3.779 (22.649)	-1.237 (14.551)
SE	2.517	2.800
Median	0.000	0.000
Min, Max	-195.60, 11.90	-55.30, 36.20

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

Alnylam Pharmaceuticals Inc.
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Table 14.3
Cardiac Biomarkers - Troponin I (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Cardiac Subpopulation: No

Subgroup Visit	Vutrisiran (HELIOS-A) (N=82)	Patisiran (HELIOS-A) (N=28)
Week 24		
Actual Value		
n	77	24
Mean (SD)	16.081 (14.534)	22.646 (27.856)
SE	1.656	5.686
Median	10.000	10.250
Min, Max	10.00, 86.10	10.00, 135.50
Change from baseline		
n	77	24
Mean (SD)	-3.770 (23.378)	-1.521 (8.636)
SE	2.664	1.763
Median	0.000	0.000
Min, Max	-195.60, 23.60	-32.70, 15.70

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

Alnylam Pharmaceuticals Inc.
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Table 14.3
Cardiac Biomarkers - Troponin I (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Cardiac Subpopulation: No

Subgroup Visit	Vutrisiran (HELIOS-A) (N=82)	Patisiran (HELIOS-A) (N=28)
Month 9		
Actual Value		
n	75	25
Mean (SD)	15.253 (12.270)	25.544 (38.375)
SE	1.417	7.675
Median	10.000	10.000
Min, Max	10.00, 82.70	10.00, 193.00
Change from baseline		
n	75	25
Mean (SD)	-4.691 (23.475)	0.664 (11.297)
SE	2.711	2.259
Median	0.000	0.000
Min, Max	-195.60, 8.70	-21.10, 36.70

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

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Table 14.3
Cardiac Biomarkers - Troponin I (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Cardiac Subpopulation: No

Subgroup Visit	Vutrisiran (HELIOS-A) (N=82)	Patisiran (HELIOS-A) (N=28)
Week 48		
Actual Value		
n	76	26
Mean (SD)	16.264 (14.721)	30.315 (69.262)
SE	1.689	13.583
Median	10.000	10.000
Min, Max	10.00, 78.30	10.00, 363.80
Change from baseline		
n	76	26
Mean (SD)	-4.703 (23.217)	5.562 (39.672)
SE	2.663	7.780
Median	0.000	0.000
Min, Max	-195.60, 12.80	-28.00, 195.60

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

Alnylam Pharmaceuticals Inc.
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Table 14.3
Cardiac Biomarkers - Troponin I (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Cardiac Subpopulation: No

Subgroup Visit	Vutrisiran (HELIOS-A) (N=82)	Patisiran (HELIOS-A) (N=28)
Week 60		
Actual Value		
n	80	23
Mean (SD)	18.811 (22.480)	15.109 (9.312)
SE	2.513	1.942
Median	10.000	10.000
Min, Max	10.00, 153.70	10.00, 41.30
Change from baseline		
n	80	23
Mean (SD)	-1.925 (8.971)	-2.770 (7.702)
SE	1.003	1.606
Median	0.000	0.000
Min, Max	-51.90, 14.20	-27.40, 8.30

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

Alnylam Pharmaceuticals Inc.
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Table 14.3
Cardiac Biomarkers - Troponin I (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Cardiac Subpopulation: No

Subgroup Visit	Vutrisiran (HELIOS-A) (N=82)	Patisiran (HELIOS-A) (N=28)
Week 72		
Actual Value		
n	77	22
Mean (SD)	16.791 (15.807)	17.118 (11.450)
SE	1.801	2.441
Median	10.000	10.600
Min, Max	10.00, 96.30	10.00, 45.10
Change from baseline		
n	77	22
Mean (SD)	-0.864 (7.427)	-2.386 (7.440)
SE	0.846	1.586
Median	0.000	0.000
Min, Max	-31.10, 20.80	-22.40, 7.30

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

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Table 14.3
Cardiac Biomarkers - Troponin I (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Cardiac Subpopulation: No

Subgroup Visit	Vutrisiran (HELIOS-A) (N=82)	Patisiran (HELIOS-A) (N=28)
Month 18		
Actual Value		
n	75	25
Mean (SD)	16.081 (14.685)	18.204 (16.382)
SE	1.696	3.276
Median	10.000	10.000
Min, Max	10.00, 88.90	10.00, 83.60
Change from baseline		
n	75	25
Mean (SD)	-4.192 (23.940)	-0.812 (9.014)
SE	2.764	1.803
Median	0.000	0.000
Min, Max	-195.60, 32.80	-22.80, 30.00

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

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Table 14.3
Cardiac Biomarkers - Troponin I (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Weight (kg): <65

Subgroup Visit	Vutrisiran (HELIOS-A) (N=46)	Patisiran (HELIOS-A) (N=15)
Baseline		
n	46	15
Mean (SD)	60.550 (193.612)	104.000 (320.708)
SE	28.547	82.806
Median	13.100	10.000
Min, Max	10.00, 1250.50	10.00, 1262.00
Week 12		
Actual Value		
n	44	15
Mean (SD)	34.582 (96.132)	157.787 (528.371)
SE	14.492	136.425
Median	10.950	13.400
Min, Max	10.00, 647.60	10.00, 2066.80
Change from baseline		
n	44	15
Mean (SD)	-0.073 (28.769)	53.787 (207.811)
SE	4.337	53.657
Median	0.000	0.000
Min, Max	-76.60, 164.00	-8.20, 804.80

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

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Table 14.3
Cardiac Biomarkers - Troponin I (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Weight (kg): <65

Subgroup Visit	Vutrisiran (HELIOS-A) (N=46)	Patisiran (HELIOS-A) (N=15)
Week 24		
Actual Value		
n	43	12
Mean (SD)	34.472 (89.108)	147.167 (451.856)
SE	13.589	130.440
Median	10.900	10.000
Min, Max	10.00, 591.00	10.00, 1581.30
Change from baseline		
n	43	12
Mean (SD)	0.133 (21.835)	26.308 (92.497)
SE	3.330	26.701
Median	0.000	0.000
Min, Max	-75.00, 107.40	-11.60, 319.30

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

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Table 14.3
Cardiac Biomarkers - Troponin I (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Weight (kg): <65

Subgroup Visit	Vutrisiran (HELIOS-A) (N=46)	Patisiran (HELIOS-A) (N=15)
Month 9		
Actual Value		
n	44	14
Mean (SD)	33.177 (81.468)	176.636 (577.997)
SE	12.282	154.476
Median	10.000	12.500
Min, Max	10.00, 541.50	10.00, 2183.70
Change from baseline		
n	44	14
Mean (SD)	-1.325 (14.751)	66.750 (246.350)
SE	2.224	65.840
Median	0.000	0.000
Min, Max	-43.20, 57.90	-17.60, 921.70

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

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Table 14.3
Cardiac Biomarkers - Troponin I (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Weight (kg): <65

Subgroup Visit	Vutrisiran (HELIOS-A) (N=46)	Patisiran (HELIOS-A) (N=15)
Week 48		
Actual Value		
n	43	15
Mean (SD)	29.753 (61.087)	83.720 (246.119)
SE	9.316	63.548
Median	10.900	10.000
Min, Max	10.00, 400.70	10.00, 971.40
Change from baseline		
n	43	15
Mean (SD)	-5.319 (17.575)	-20.280 (75.350)
SE	2.680	19.455
Median	0.000	0.000
Min, Max	-82.90, 30.00	-290.60, 20.10

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

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Table 14.3
Cardiac Biomarkers - Troponin I (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Weight (kg): <65

Subgroup Visit	Vutrisiran (HELIOS-A) (N=46)	Patisiran (HELIOS-A) (N=15)
Week 60		
Actual Value		
n	43	13
Mean (SD)	32.216 (75.916)	140.792 (444.826)
SE	11.577	123.373
Median	10.700	10.000
Min, Max	10.00, 499.00	10.00, 1620.80
Change from baseline		
n	43	13
Mean (SD)	-2.856 (11.061)	25.731 (100.307)
SE	1.687	27.820
Median	0.000	0.000
Min, Max	-46.10, 16.70	-20.20, 358.80

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

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Table 14.3
Cardiac Biomarkers - Troponin I (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Weight (kg): <65

Subgroup Visit	Vutrisiran (HELIOS-A) (N=46)	Patisiran (HELIOS-A) (N=15)
Week 72		
Actual Value		
n	44	13
Mean (SD)	29.661 (54.306)	95.146 (280.857)
SE	8.187	77.896
Median	10.000	10.000
Min, Max	10.00, 354.80	10.00, 1029.20
Change from baseline		
n	44	13
Mean (SD)	-4.841 (24.445)	-22.062 (63.982)
SE	3.685	17.745
Median	0.000	0.000
Min, Max	-128.80, 34.00	-232.80, 4.90

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

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Table 14.3
Cardiac Biomarkers - Troponin I (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Weight (kg): <65

Subgroup Visit	Vutrisiran (HELIOS-A) (N=46)	Patisiran (HELIOS-A) (N=15)
Month 18		
Actual Value		
n	42	14
Mean (SD)	29.448 (57.522)	20.664 (20.684)
SE	8.876	5.528
Median	10.000	10.000
Min, Max	10.00, 366.90	10.00, 83.60
Change from baseline		
n	42	14
Mean (SD)	-5.948 (23.596)	-0.621 (11.859)
SE	3.641	3.169
Median	0.000	0.000
Min, Max	-116.70, 45.50	-28.10, 30.00

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

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Table 14.3
Cardiac Biomarkers - Troponin I (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Weight (kg): ≥65

Subgroup Visit	Vutrisiran (HELIOS-A) (N=76)	Patisiran (HELIOS-A) (N=27)
Baseline		
n	76	27
Mean (SD)	22.254 (28.997)	47.922 (77.518)
SE	3.326	14.918
Median	10.000	17.900
Min, Max	10.00, 205.60	10.00, 325.40
Week 12		
Actual Value		
n	75	25
Mean (SD)	18.707 (15.343)	59.628 (112.673)
SE	1.772	22.535
Median	10.000	17.400
Min, Max	10.00, 79.10	10.00, 443.70
Change from baseline		
n	75	25
Mean (SD)	-3.069 (24.024)	9.456 (43.638)
SE	2.774	8.728
Median	0.000	0.000
Min, Max	-195.60, 23.10	-55.30, 191.10

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

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Table 14.3
Cardiac Biomarkers - Troponin I (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Weight (kg): ≥65

Subgroup Visit	Vutrisiran (HELIOS-A) (N=76)	Patisiran (HELIOS-A) (N=27)
Week 24		
Actual Value		
n	71	24
Mean (SD)	17.761 (15.183)	53.250 (99.969)
SE	1.802	20.406
Median	10.000	14.650
Min, Max	10.00, 86.10	10.00, 398.30
Change from baseline		
n	71	24
Mean (SD)	-3.265 (24.478)	4.650 (31.191)
SE	2.905	6.367
Median	0.000	0.000
Min, Max	-195.60, 20.00	-32.70, 145.70

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

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Table 14.3
Cardiac Biomarkers - Troponin I (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Weight (kg): ≥65

Subgroup Visit	Vutrisiran (HELIOS-A) (N=76)	Patisiran (HELIOS-A) (N=27)
Month 9		
Actual Value		
n	68	24
Mean (SD)	18.307 (15.644)	47.138 (100.334)
SE	1.897	20.481
Median	10.000	13.200
Min, Max	10.00, 82.70	10.00, 481.40
Change from baseline		
n	68	24
Mean (SD)	-2.893 (25.232)	7.858 (33.765)
SE	3.060	6.892
Median	0.000	0.000
Min, Max	-195.60, 27.90	-21.10, 156.00

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

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Table 14.3
Cardiac Biomarkers - Troponin I (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Weight (kg): ≥65

Subgroup Visit	Vutrisiran (HELIOS-A) (N=76)	Patisiran (HELIOS-A) (N=27)
Week 48		
Actual Value		
n	71	24
Mean (SD)	18.620 (17.006)	71.242 (150.122)
SE	2.018	30.644
Median	10.000	13.350
Min, Max	10.00, 80.20	10.00, 605.40
Change from baseline		
n	71	24
Mean (SD)	-3.462 (24.846)	22.733 (71.856)
SE	2.949	14.667
Median	0.000	0.000
Min, Max	-195.60, 34.80	-28.00, 280.00

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

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Table 14.3
Cardiac Biomarkers - Troponin I (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Weight (kg): ≥65

Subgroup Visit	Vutrisiran (HELIOS-A) (N=76)	Patisiran (HELIOS-A) (N=27)
Week 60		
Actual Value		
n	75	22
Mean (SD)	20.267 (23.026)	61.286 (145.949)
SE	2.659	31.116
Median	10.000	13.650
Min, Max	10.00, 153.70	10.00, 635.80
Change from baseline		
n	75	22
Mean (SD)	-1.509 (9.187)	16.468 (68.961)
SE	1.061	14.703
Median	0.000	0.000
Min, Max	-51.90, 17.40	-27.40, 310.40

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

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Table 14.3
Cardiac Biomarkers - Troponin I (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Weight (kg): ≥65

Subgroup Visit	Vutrisiran (HELIOS-A) (N=76)	Patisiran (HELIOS-A) (N=27)
Week 72		
Actual Value		
n	70	22
Mean (SD)	18.494 (16.741)	76.764 (186.951)
SE	2.001	39.858
Median	10.000	15.850
Min, Max	10.00, 96.30	10.00, 665.40
Change from baseline		
n	70	22
Mean (SD)	-0.151 (7.612)	31.945 (108.707)
SE	0.910	23.176
Median	0.000	0.000
Min, Max	-27.40, 20.80	-22.40, 412.80

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

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Table 14.3
Cardiac Biomarkers - Troponin I (ng/L): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Weight (kg): ≥65

Subgroup Visit	Vutrisiran (HELIOS-A) (N=76)	Patisiran (HELIOS-A) (N=27)
Month 18		
Actual Value		
n	70	22
Mean (SD)	17.604 (15.187)	84.827 (220.035)
SE	1.815	46.912
Median	10.000	15.250
Min, Max	10.00, 88.90	10.00, 871.30
Change from baseline		
n	70	22
Mean (SD)	-3.816 (24.840)	40.009 (145.830)
SE	2.969	31.091
Median	0.000	0.000
Min, Max	-195.60, 32.80	-22.80, 618.70

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

Subgruppenanalysen zum Endpunkt „Veränderung des Invaliditätsgrades gemessen anhand des R-ODS“

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ALN-TTRSC02-002

Table 6.2
Rasch-built Overall Disability Scale (R-ODS): Change from Baseline to Month 18, MMRM Model
Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A) Subgroup Analysis
mITT Population

Subgroup Visit	LS Mean (95% CI) Vutrisiran (HELIOS-A) (N=122)	LS Mean (95% CI) Patisiran (HELIOS-A) (N=42)	LS Mean Difference (Vutrisiran-Patisiran) (95% CI), p-value	Standardized Effect Size (95% CI)
Age (years)				
<65	75	30		
Month 9	-0.89 (-2.17, 0.39)	-1.87 (-3.90, 0.16)	0.98 (-1.41, 3.37), 0.4200	0.19 (-0.24, 0.61)
Month 18	-1.61 (-2.89, -0.34)	-1.30 (-3.33, 0.73)	-0.31 (-2.70, 2.07), 0.7954	-0.05 (-0.48, 0.37)
≥65	43	10		
Month 9	0.41 (-1.24, 2.07)	-1.71 (-5.06, 1.63)	2.13 (-1.59, 5.85), 0.2607	0.32 (-0.36, 1.01)
Month 18	-0.31 (-1.96, 1.34)	-1.14 (-4.51, 2.22)	0.83 (-2.90, 4.57), 0.6602	0.15 (-0.56, 0.86)
p-value of Treatment*Age	0.5939			

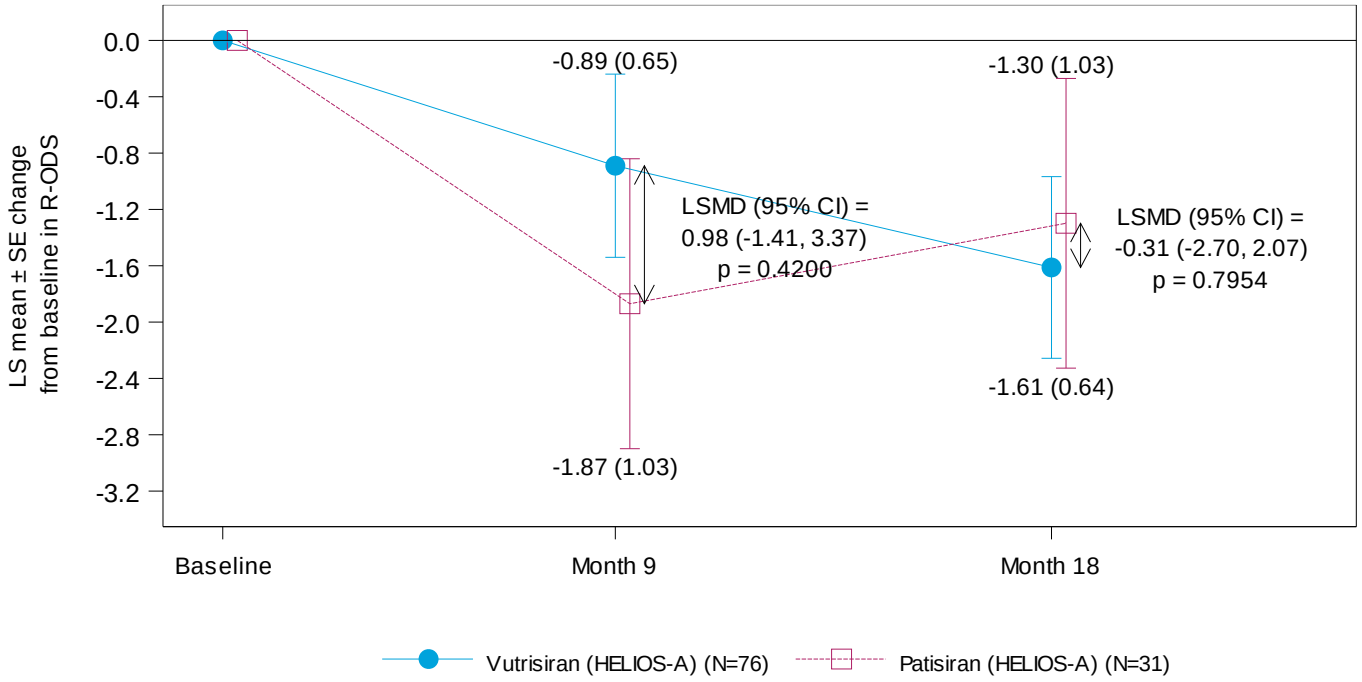
R-ODS score = composite of 24 disability questions; higher scores indicate lower disability (range = 0 to 48). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.
LS estimates and p-value derived from mixed-effects model for repeated measures (MMRM), controlling for categorical factors (treatment, visit), the subgroup variable, continuous covariate (baseline value), and interaction (treatment by visit, treatment by subgroup).
Standardized effect size (d) = LS mean difference/estimated pooled standard deviation with the small sample bias correction.

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

Alnylam Pharmaceuticals Inc.
ALN-TTRSC02-002

Rasch-built Overall Disability Scale (R-ODS): Change from Baseline Over Time Series Plot
Subgroup Analysis: Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A)
mITT Population

Age (years): <65



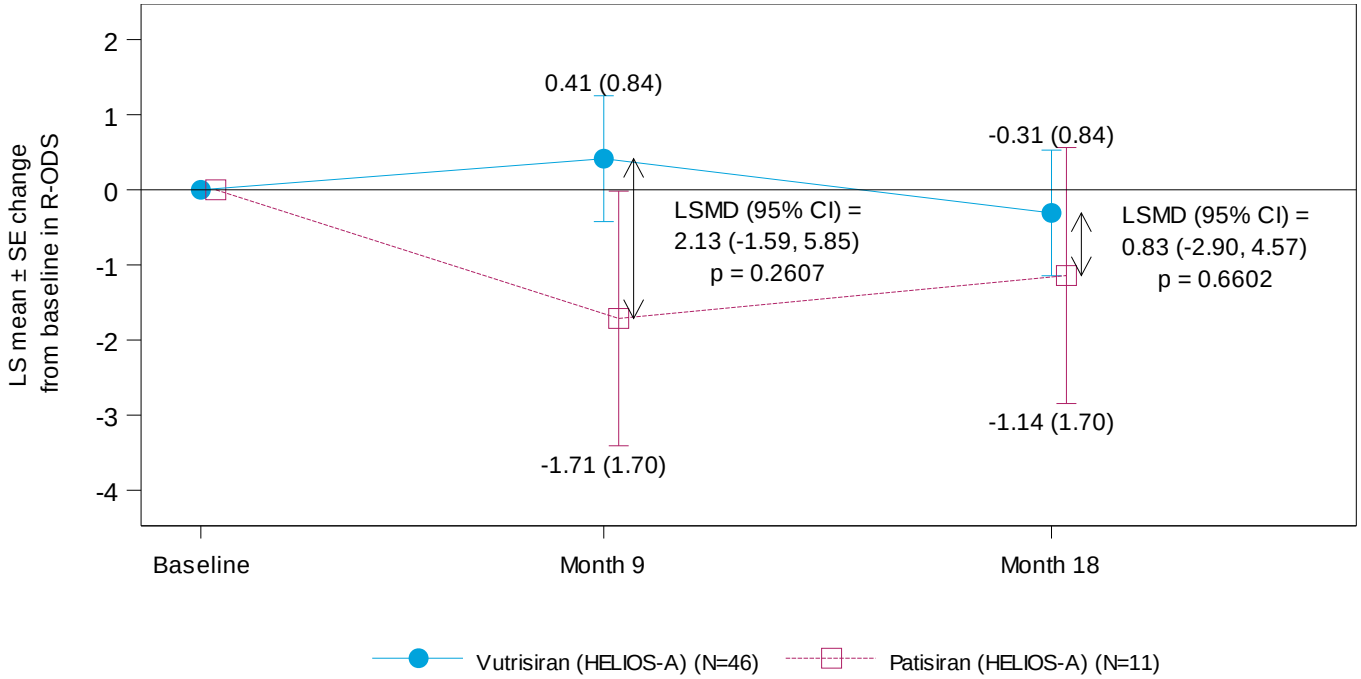
N evaluable			
Vutrisiran	76	74	74
Patisiran	31	30	29

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

Alnylam Pharmaceuticals Inc.
ALN-TTRSC02-002

Rasch-built Overall Disability Scale (R-ODS): Change from Baseline Over Time Series Plot
Subgroup Analysis: Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A)
mITT Population

Age (years): ≥65



N evaluable			
Vutrisiran	46	41	40
Patisiran	11	10	9

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

Alnylam Pharmaceuticals Inc.
ALN-TTRSC02-002

Table 6.2
Rasch-built Overall Disability Scale (R-ODS): Change from Baseline to Month 18, MMRM Model
Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A) Subgroup Analysis
mITT Population

Subgroup Visit	LS Mean (95% CI) Vutrisiran (HELIOS-A) (N=122)	LS Mean (95% CI) Patisiran (HELIOS-A) (N=42)	LS Mean Difference (Vutrisiran-Patisiran) (95% CI), p-value	Standardized Effect Size (95% CI)
Sex				
Male	77	25		
Month 9	-0.83 (-2.10, 0.44)	-1.87 (-4.08, 0.34)	1.03 (-1.52, 3.58), 0.4243	0.18 (-0.27, 0.63)
Month 18	-1.56 (-2.80, -0.31)	-1.29 (-3.49, 0.91)	-0.26 (-2.79, 2.26), 0.8370	-0.04 (-0.51, 0.42)
Female	41	15		
Month 9	0.37 (-1.31, 2.05)	-1.75 (-4.53, 1.02)	2.12 (-1.12, 5.36), 0.1985	0.36 (-0.23, 0.95)
Month 18	-0.36 (-2.02, 1.30)	-1.18 (-3.91, 1.55)	0.82 (-2.38, 4.02), 0.6125	0.16 (-0.42, 0.75)
p-value of Treatment*Sex	0.5830			

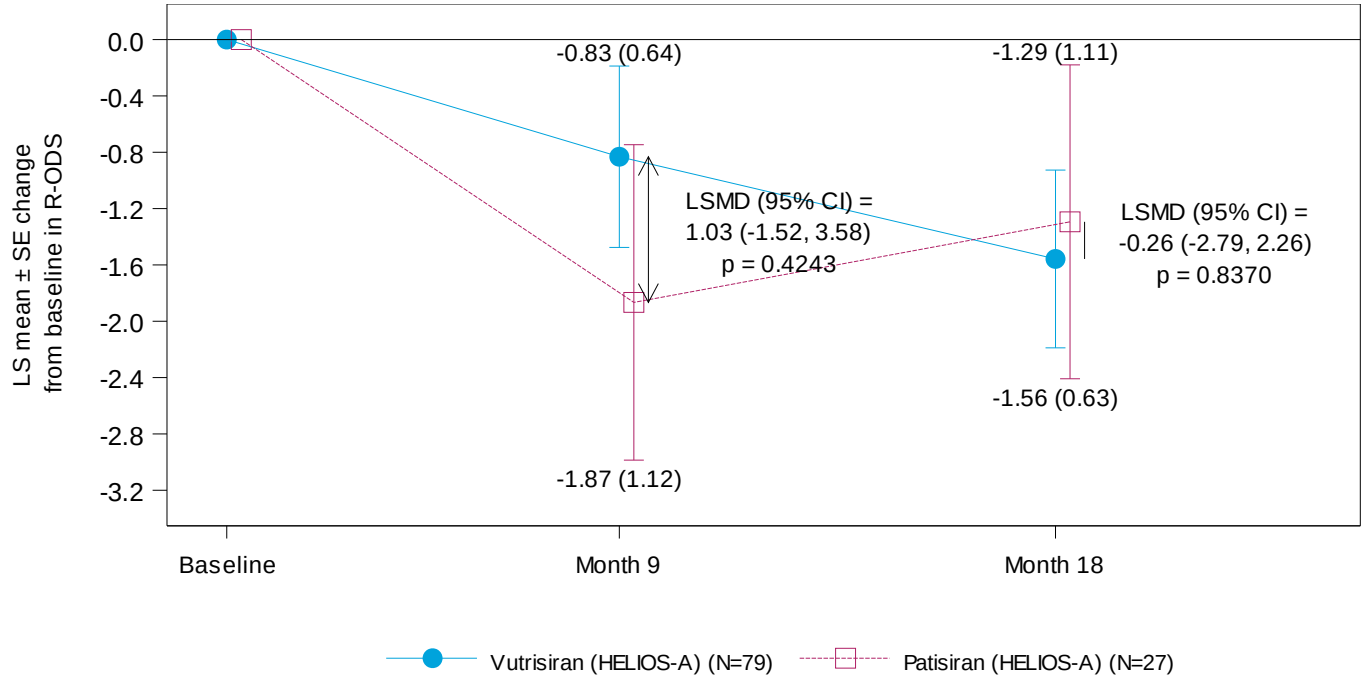
R-ODS score = composite of 24 disability questions; higher scores indicate lower disability (range = 0 to 48). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.
LS estimates and p-value derived from mixed-effects model for repeated measures (MMRM), controlling for categorical factors (treatment, visit), the subgroup variable, continuous covariate (baseline value), and interaction (treatment by visit, treatment by subgroup).
Standardized effect size (d) = LS mean difference/estimated pooled standard deviation with the small sample bias correction.

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

Alnylam Pharmaceuticals Inc.
ALN-TTRSC02-002

Rasch-built Overall Disability Scale (R-ODS): Change from Baseline Over Time Series Plot
Subgroup Analysis: Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A)
mITT Population

Sex: Male



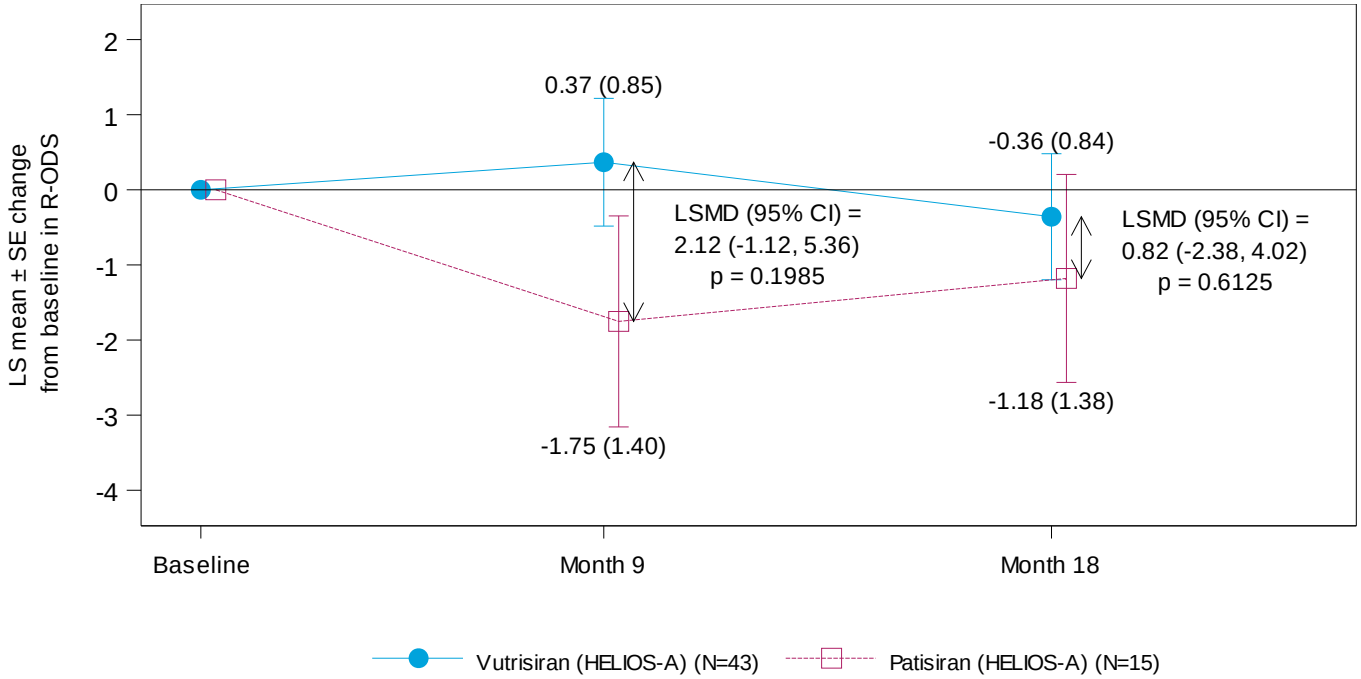
N evaluable			
Vutrisiran	79	75	74
Patisiran	27	25	23

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

Alnylam Pharmaceuticals Inc.
ALN-TTRSC02-002

Rasch-built Overall Disability Scale (R-ODS): Change from Baseline Over Time Series Plot
Subgroup Analysis: Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A)
mITT Population

Sex: Female



N evaluable			
Vutrisiran	43	40	40
Patisiran	15	15	15

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

Alnylam Pharmaceuticals Inc.
ALN-TTRSC02-002

Rasch-built Overall Disability Scale (R-ODS): Change from Baseline to Month 18, MMRM Model
Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A) Subgroup Analysis
mITT Population

Subgroup Visit	LS Mean (95% CI) Vutrisiran (HELIOS-A) (N=122)	LS Mean (95% CI) Patisiran (HELIOS-A) (N=42)	LS Mean Difference (Vutrisiran-Patisiran) (95% CI), p-value	Standardized Effect Size (95% CI)
Race				
White	83	28		
Month 9	-0.58 (-1.82, 0.65)	-1.76 (-3.86, 0.35)	1.17 (-1.27, 3.61), 0.3441	0.23 (-0.20, 0.66)
Month 18	-1.31 (-2.52, -0.09)	-1.19 (-3.27, 0.90)	-0.12 (-2.54, 2.29), 0.9208	-0.02 (-0.46, 0.41)
All Other Races	35	12		
Month 9	-0.01 (-1.83, 1.80)	-1.98 (-5.08, 1.11)	1.97 (-1.63, 5.56), 0.2815	0.27 (-0.37, 0.92)
Month 18	-0.74 (-2.54, 1.07)	-1.41 (-4.51, 1.69)	0.67 (-2.92, 4.27), 0.7125	0.10 (-0.57, 0.77)
p-value of Treatment*Race	0.7065			

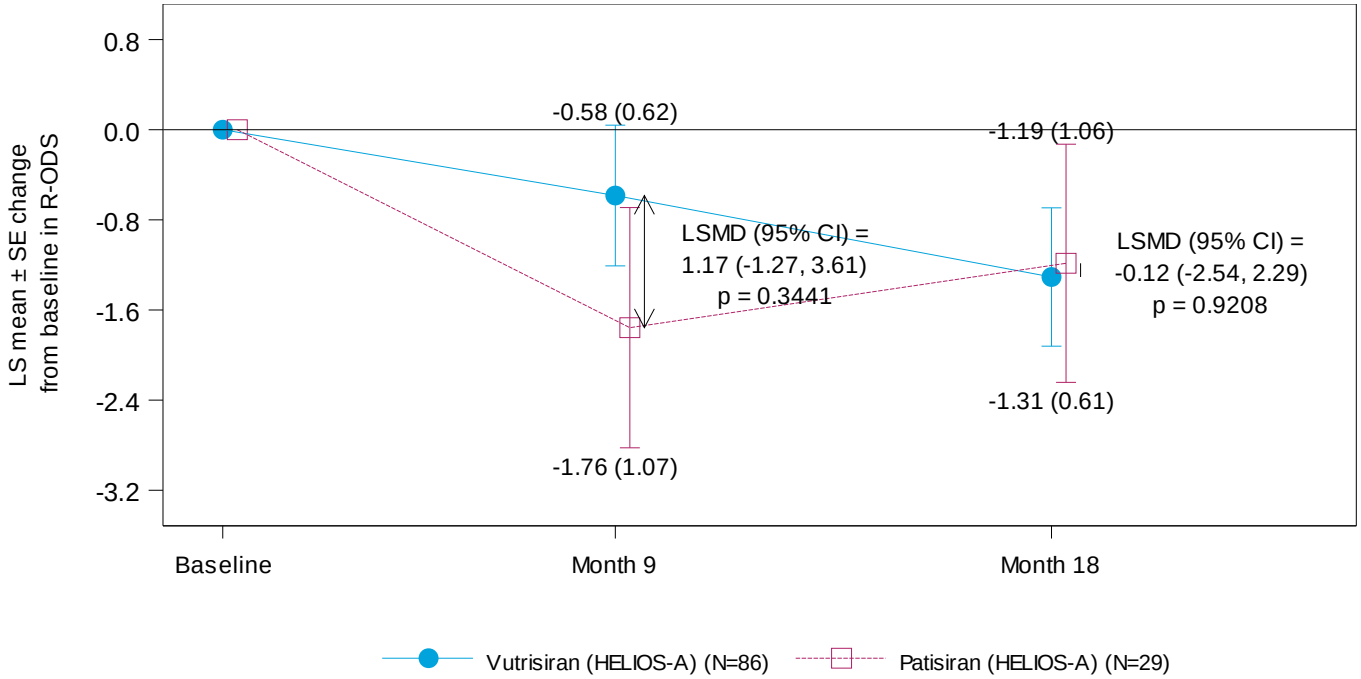
R-ODS score = composite of 24 disability questions; higher scores indicate lower disability (range = 0 to 48). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.
LS estimates and p-value derived from mixed-effects model for repeated measures (MMRM), controlling for categorical factors (treatment, visit), the subgroup variable, continuous covariate (baseline value), and interaction (treatment by visit, treatment by subgroup).
Standardized effect size (d) = LS mean difference/estimated pooled standard deviation with the small sample bias correction.

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

Alnylam Pharmaceuticals Inc.
ALN-TTRSC02-002

Rasch-built Overall Disability Scale (R-ODS): Change from Baseline Over Time Series Plot
Subgroup Analysis: Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A)
mITT Population

Race: White



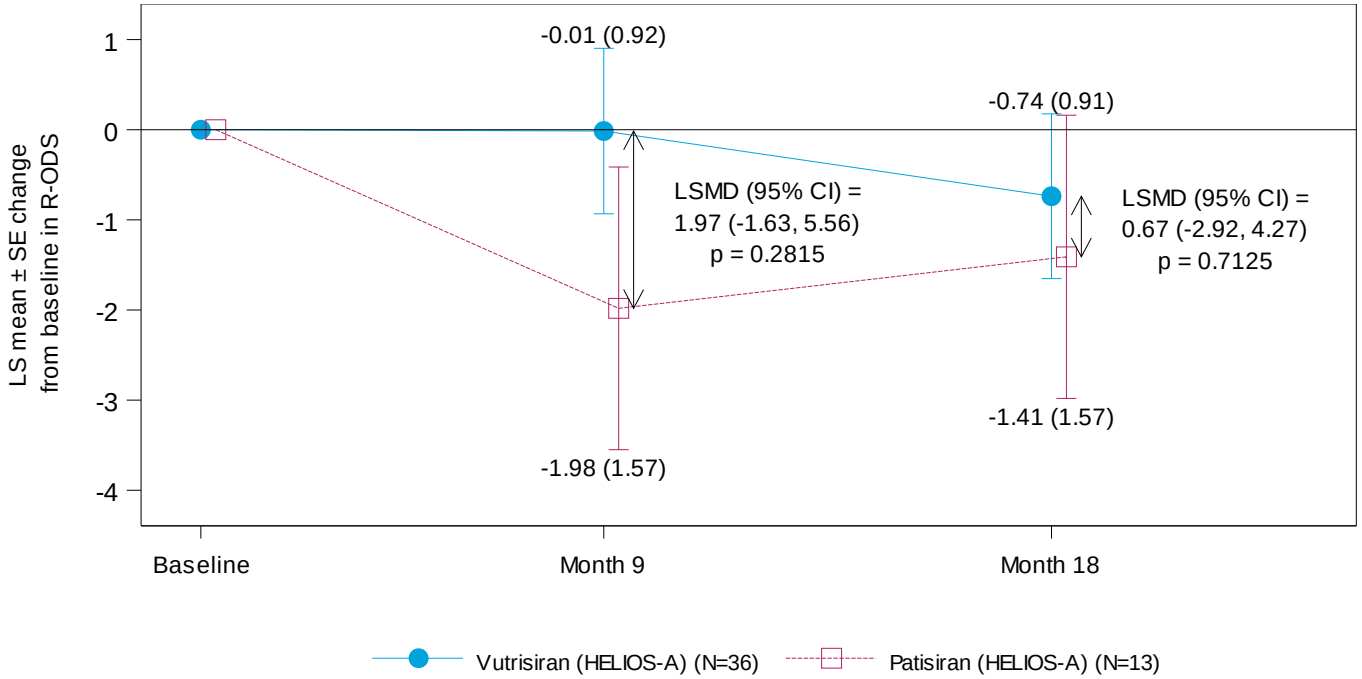
N evaluable			
Vutrisiran	86	81	81
Patisiran	29	28	27

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

Alnylam Pharmaceuticals Inc.
ALN-TTRSC02-002

Rasch-built Overall Disability Scale (R-ODS): Change from Baseline Over Time Series Plot
Subgroup Analysis: Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A)
mITT Population

Race: All Other Races



N evaluable

Vutrisiran	36	34	33
Patisiran	13	12	11

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

Alnylam Pharmaceuticals Inc.
ALN-TTRSC02-002

Table 6.2
Rasch-built Overall Disability Scale (R-ODS): Change from Baseline to Month 18, MMRM Model
Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A) Subgroup Analysis
mITT Population

Subgroup Visit	LS Mean (95% CI) Vutrisiran (HELIOS-A) (N=122)	LS Mean (95% CI) Patisiran (HELIOS-A) (N=42)	LS Mean Difference (Vutrisiran-Patisiran) (95% CI), p-value	Standardized Effect Size (95% CI)
Region				
North America	27	8		
Month 9	0.78 (-1.29, 2.84)	-3.43 (-7.14, 0.28)	4.21 (-0.02, 8.43), 0.0509	0.68 (-0.11, 1.47)
Month 18	0.06 (-1.99, 2.11)	-2.89 (-6.60, 0.83)	2.94 (-1.28, 7.16), 0.1707	0.46 (-0.37, 1.28)
Western Europe	39	18		
Month 9	-0.98 (-2.69, 0.72)	0.19 (-2.34, 2.72)	-1.17 (-4.22, 1.87), 0.4483	-0.25 (-0.80, 0.31)
Month 18	-1.71 (-3.39, -0.03)	0.73 (-1.76, 3.22)	-2.44 (-5.44, 0.56), 0.1103	-0.53 (-1.09, 0.03)
Rest of World	52	14		
Month 9	-0.59 (-2.09, 0.92)	-3.48 (-6.32, -0.64)	2.89 (-0.32, 6.10), 0.0771	0.45 (-0.14, 1.04)
Month 18	-1.31 (-2.80, 0.18)	-2.94 (-5.76, -0.11)	1.63 (-1.57, 4.82), 0.3162	0.27 (-0.33, 0.88)
p-value of Treatment*Region	0.0574			

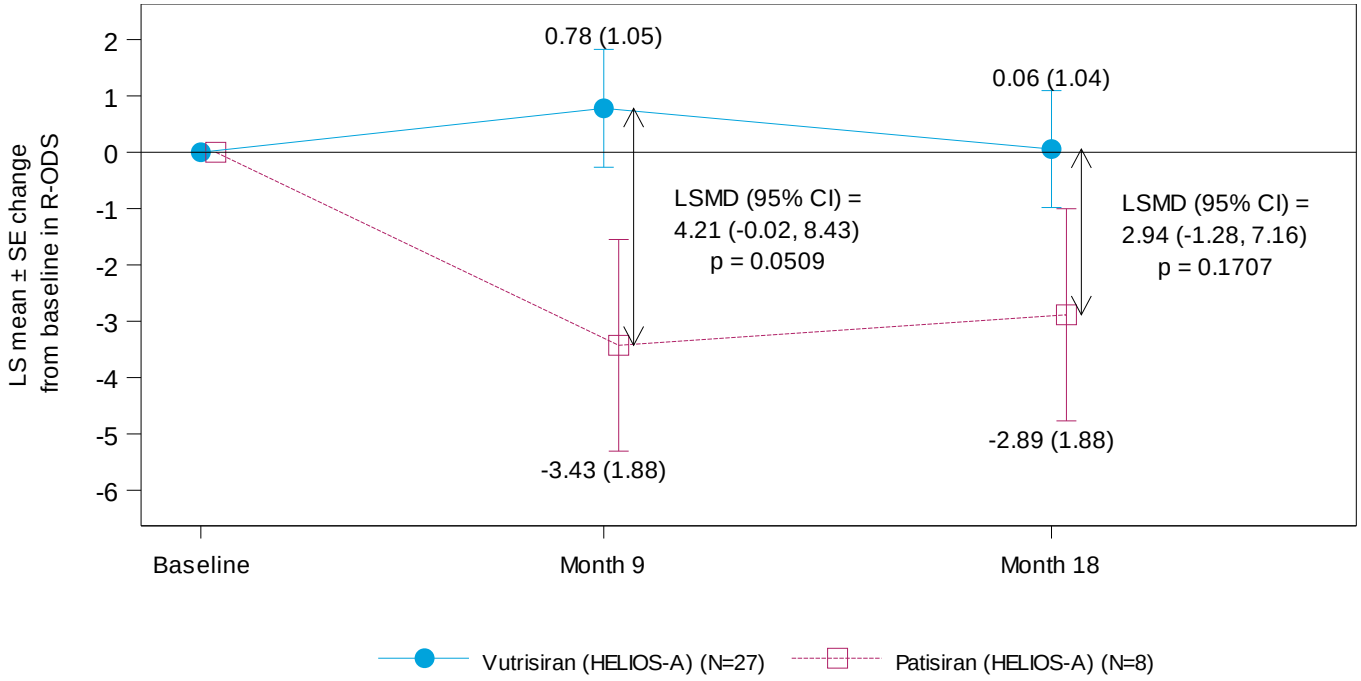
R-ODS score = composite of 24 disability questions; higher scores indicate lower disability (range = 0 to 48). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.
LS estimates and p-value derived from mixed-effects model for repeated measures (MMRM), controlling for categorical factors (treatment, visit), the subgroup variable, continuous covariate (baseline value), and interaction (treatment by visit, treatment by subgroup).
Standardized effect size (d) = LS mean difference/estimated pooled standard deviation with the small sample bias correction.

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

Alnylam Pharmaceuticals Inc.
ALN-TTRSC02-002

Rasch-built Overall Disability Scale (R-ODS): Change from Baseline Over Time Series Plot
Subgroup Analysis: Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A)
mITT Population

Region: North America



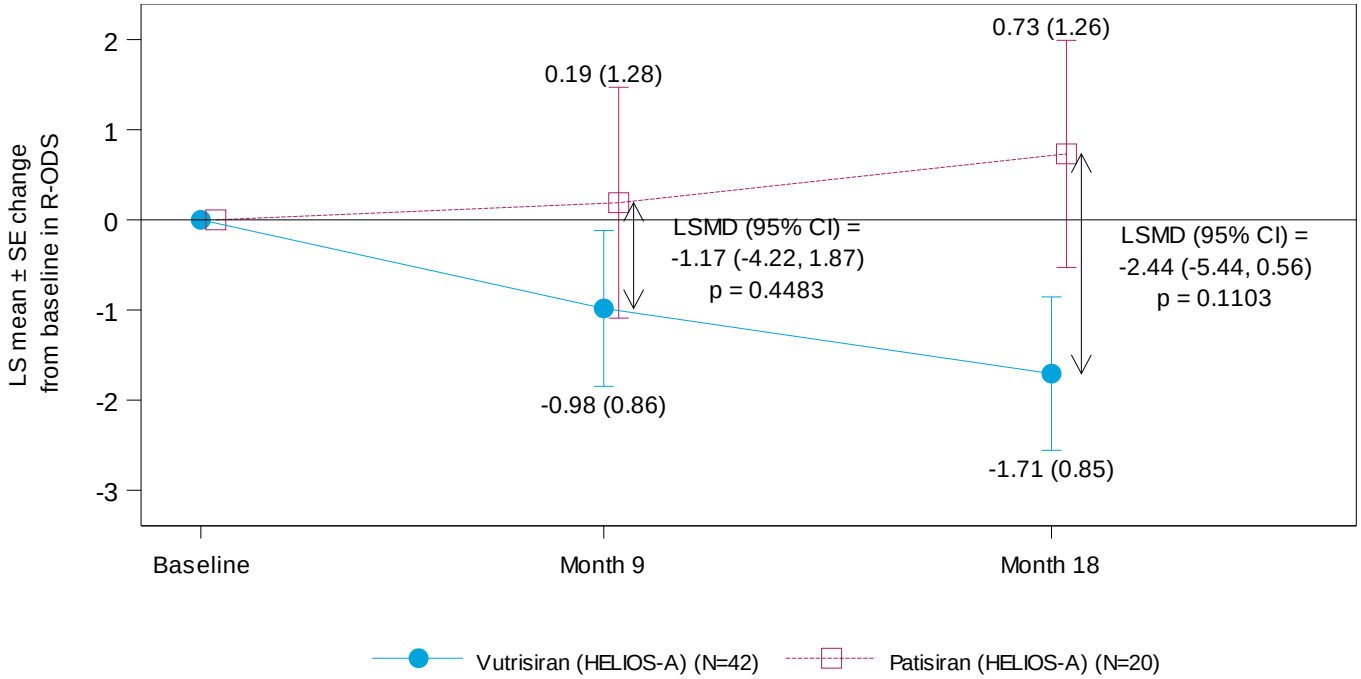
N evaluable			
Vutrisiran	27	25	25
Patisiran	8	8	7

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

Alnylam Pharmaceuticals Inc.
ALN-TTRSC02-002

Rasch-built Overall Disability Scale (R-ODS): Change from Baseline Over Time Series Plot
Subgroup Analysis: Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A)
mITT Population

Region: Western Europe



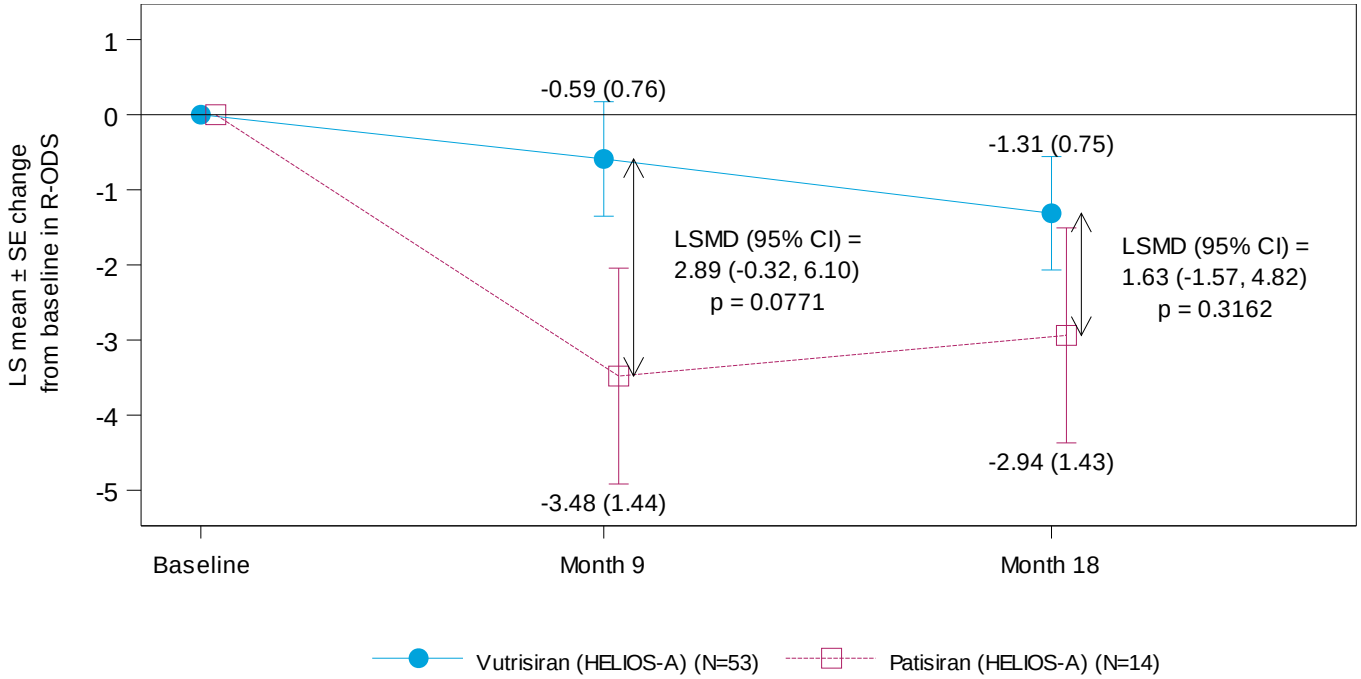
N evaluable			
Vutrisiran	42	38	39
Patisiran	20	18	18

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

Alnylam Pharmaceuticals Inc.
ALN-TTRSC02-002

Rasch-built Overall Disability Scale (R-ODS): Change from Baseline Over Time Series Plot
Subgroup Analysis: Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A)
mITT Population

Region: Rest of World



N evaluable			
Vutrisiran	53	52	50
Patisiran	14	14	13

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

Alnylam Pharmaceuticals Inc.
ALN-TTRSC02-002

Table 6.2
Rasch-built Overall Disability Scale (R-ODS): Change from Baseline to Month 18, MMRM Model
Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A) Subgroup Analysis
mITT Population

Subgroup Visit	LS Mean (95% CI) Vutrisiran (HELIOS-A) (N=122)	LS Mean (95% CI) Patisiran (HELIOS-A) (N=42)	LS Mean Difference (Vutrisiran-Patisiran) (95% CI), p-value	Standardized Effect Size (95% CI)
Baseline NIS				
<50	77	27		
Month 9	0.93 (-0.44, 2.29)	-0.38 (-2.54, 1.78)	1.31 (-1.13, 3.75), 0.2916	0.24 (-0.20, 0.67)
Month 18	0.22 (-1.12, 1.55)	0.21 (-1.90, 2.32)	0.01 (-2.36, 2.38), 0.9937	0.00 (-0.44, 0.44)
≥50	41	13		
Month 9	-2.85 (-4.77, -0.93)	-4.55 (-7.56, -1.54)	1.69 (-1.64, 5.03), 0.3172	0.27 (-0.35, 0.89)
Month 18	-3.56 (-5.45, -1.68)	-3.96 (-6.94, -0.98)	0.40 (-2.89, 3.69), 0.8121	0.07 (-0.57, 0.70)
p-value of Treatment*Baseline NIS	0.8443			

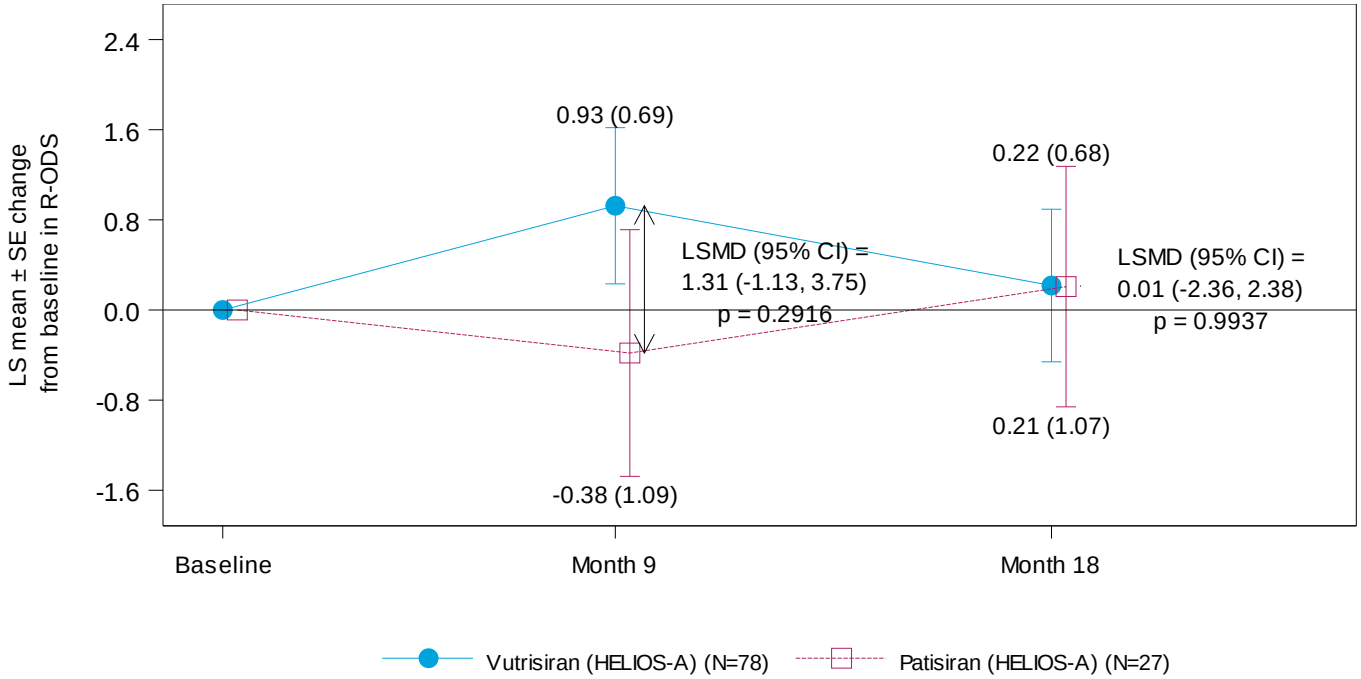
R-ODS score = composite of 24 disability questions; higher scores indicate lower disability (range = 0 to 48). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.
LS estimates and p-value derived from mixed-effects model for repeated measures (MMRM), controlling for categorical factors (treatment, visit), the subgroup variable, continuous covariate (baseline value), and interaction (treatment by visit, treatment by subgroup).
Standardized effect size (d) = LS mean difference/estimated pooled standard deviation with the small sample bias correction.

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

Alnylam Pharmaceuticals Inc.
ALN-TTRSC02-002

Rasch-built Overall Disability Scale (R-ODS): Change from Baseline Over Time Series Plot
Subgroup Analysis: Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A)
mITT Population

Baseline NIS: <50



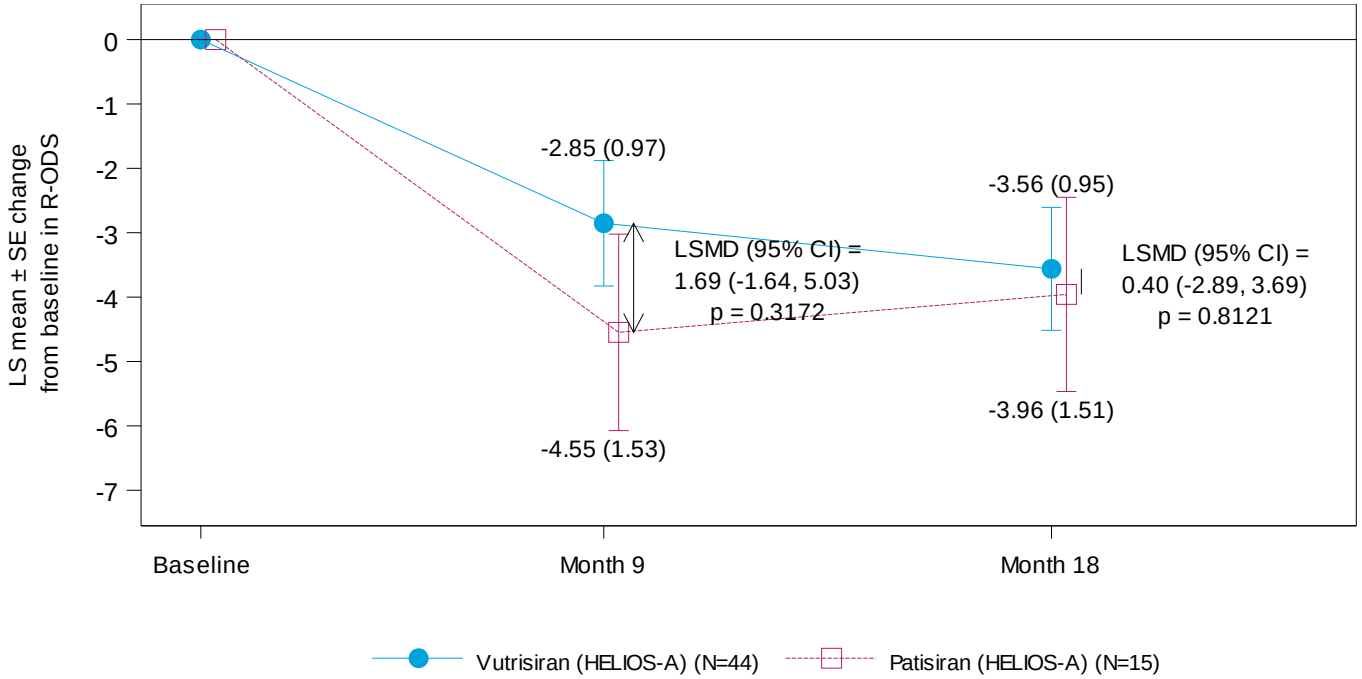
N evaluable			
Vutrisiran	78	77	75
Patisiran	27	27	26

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

Alnylam Pharmaceuticals Inc.
ALN-TTRSC02-002

Rasch-built Overall Disability Scale (R-ODS): Change from Baseline Over Time Series Plot
Subgroup Analysis: Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A)
mITT Population

Baseline NIS: ≥50



N evaluable			
Vutrisiran	44	38	39
Patisiran	15	13	12

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

Alnylam Pharmaceuticals Inc.
ALN-TTRSC02-002

Table 6.2
Rasch-built Overall Disability Scale (R-ODS): Change from Baseline to Month 18, MMRM Model
Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A) Subgroup Analysis
mITT Population

Subgroup Visit	LS Mean (95% CI) Vutrisiran (HELIOS-A) (N=122)	LS Mean (95% CI) Patisiran (HELIOS-A) (N=42)	LS Mean Difference (Vutrisiran-Patisiran) (95% CI), p-value	Standardized Effect Size (95% CI)
Previous Tetramer Stabilizer Use				
Yes	74	32		
Month 9	-0.77 (-2.04, 0.51)	-0.89 (-2.86, 1.08)	0.12 (-2.23, 2.47), 0.9195	0.02 (-0.39, 0.43)
Month 18	-1.50 (-2.75, -0.25)	-0.34 (-2.27, 1.58)	-1.15 (-3.45, 1.15), 0.3240	-0.21 (-0.63, 0.21)
No	44	8		
Month 9	0.17 (-1.43, 1.78)	-5.60 (-9.31, -1.89)	5.78 (1.74, 9.81), 0.0053	1.00 (0.23, 1.77)
Month 18	-0.55 (-2.13, 1.02)	-5.06 (-8.77, -1.35)	4.50 (0.47, 8.53), 0.0288	0.77 (-0.03, 1.57)
p-value of Treatment*Previous Tetramer Stabilizer Use	0.0137			

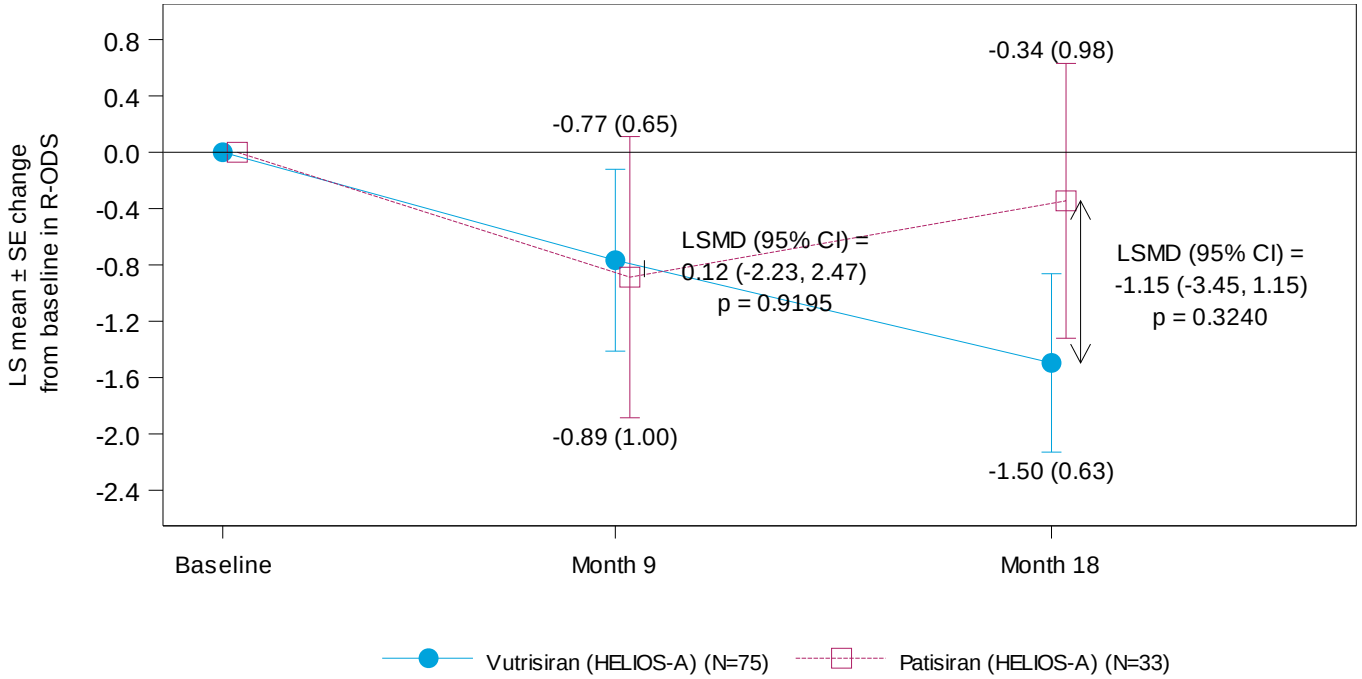
R-ODS score = composite of 24 disability questions; higher scores indicate lower disability (range = 0 to 48). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.
LS estimates and p-value derived from mixed-effects model for repeated measures (MMRM), controlling for categorical factors (treatment, visit), the subgroup variable, continuous covariate (baseline value), and interaction (treatment by visit, treatment by subgroup).
Standardized effect size (d) = LS mean difference/estimated pooled standard deviation with the small sample bias correction.

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

Alnylam Pharmaceuticals Inc.
ALN-TTRSC02-002

Rasch-built Overall Disability Scale (R-ODS): Change from Baseline Over Time Series Plot
Subgroup Analysis: Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A)
mITT Population

Previous Tetramer Stabilizer Use: Yes



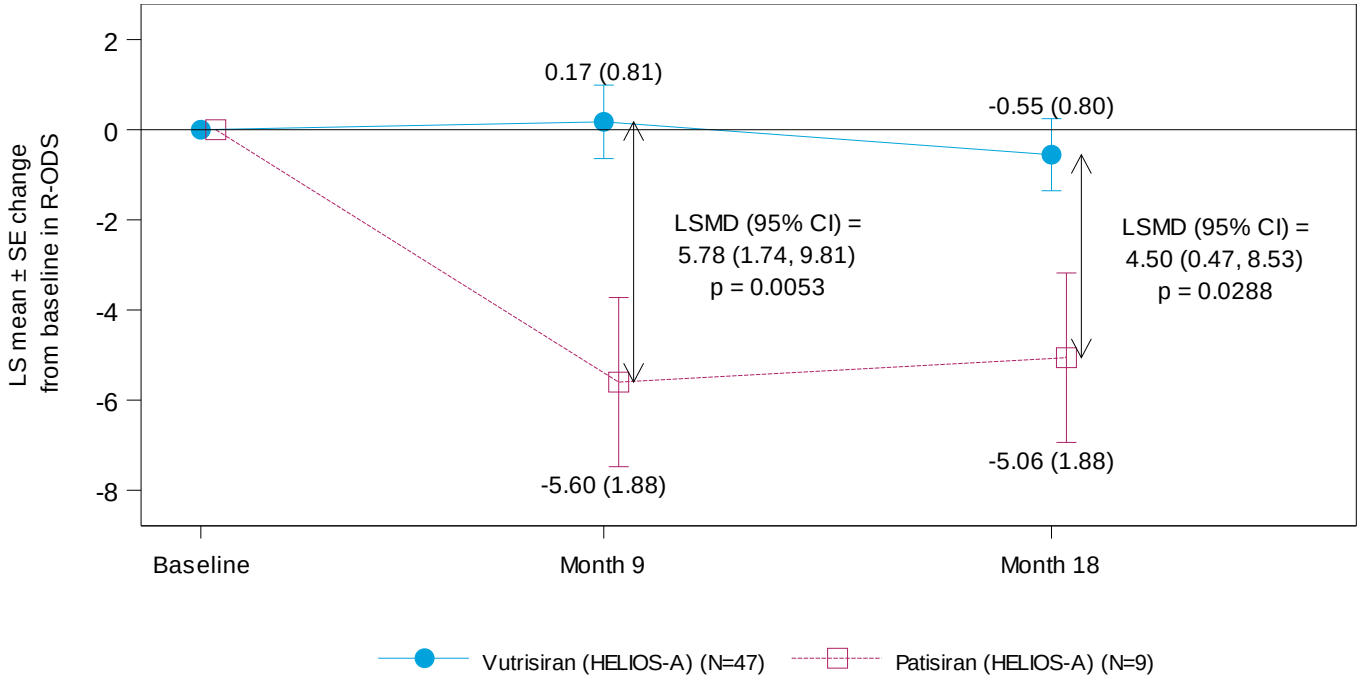
N evaluable			
Vutrisiran	75	73	71
Patisiran	33	32	31

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

Alnylam Pharmaceuticals Inc.
ALN-TTRSC02-002

Rasch-built Overall Disability Scale (R-ODS): Change from Baseline Over Time Series Plot
Subgroup Analysis: Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A)
mITT Population

Previous Tetramer Stabilizer Use: No



N evaluable			
Vutrisiran	47	42	43
Patisiran	9	8	7

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

Alnylam Pharmaceuticals Inc.
ALN-TTRSC02-002

Table 6.2
Rasch-built Overall Disability Scale (R-ODS): Change from Baseline to Month 18, MMRM Model
Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A) Subgroup Analysis
mITT Population

Subgroup Visit	LS Mean (95% CI) Vutrisiran (HELIOS-A) (N=122)	LS Mean (95% CI) Patisiran (HELIOS-A) (N=42)	LS Mean Difference (Vutrisiran-Patisiran) (95% CI), p-value	Standardized Effect Size (95% CI)
Genotype				
V30M	53	20		
Month 9	-0.55 (-2.04, 0.95)	-0.52 (-2.95, 1.90)	-0.02 (-2.87, 2.82), 0.9863	-0.01 (-0.52, 0.51)
Month 18	-1.27 (-2.74, 0.20)	0.02 (-2.36, 2.41)	-1.29 (-4.10, 1.51), 0.3630	-0.28 (-0.79, 0.23)
non-V30M	65	20		
Month 9	-0.31 (-1.67, 1.05)	-3.13 (-5.56, -0.70)	2.82 (0.03, 5.60), 0.0472	0.41 (-0.09, 0.91)
Month 18	-1.03 (-2.37, 0.31)	-2.58 (-5.01, -0.15)	1.55 (-1.23, 4.33), 0.2733	0.24 (-0.28, 0.76)
p-value of Treatment*Genotype	0.1373			

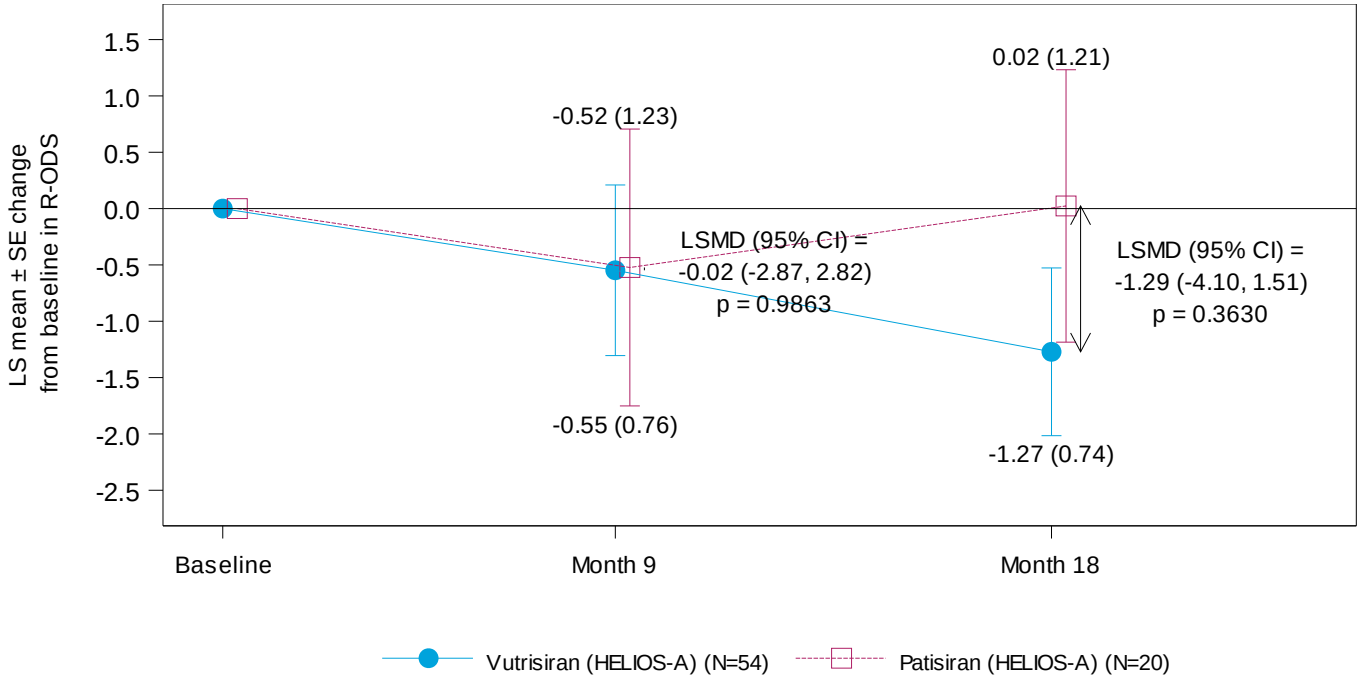
R-ODS score = composite of 24 disability questions; higher scores indicate lower disability (range = 0 to 48). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.
LS estimates and p-value derived from mixed-effects model for repeated measures (MMRM), controlling for categorical factors (treatment, visit), the subgroup variable, continuous covariate (baseline value), and interaction (treatment by visit, treatment by subgroup).
Standardized effect size (d) = LS mean difference/estimated pooled standard deviation with the small sample bias correction.

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

Alnylam Pharmaceuticals Inc.
ALN-TTRSC02-002

Rasch-built Overall Disability Scale (R-ODS): Change from Baseline Over Time Series Plot
Subgroup Analysis: Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A)
mITT Population

Genotype: V30M



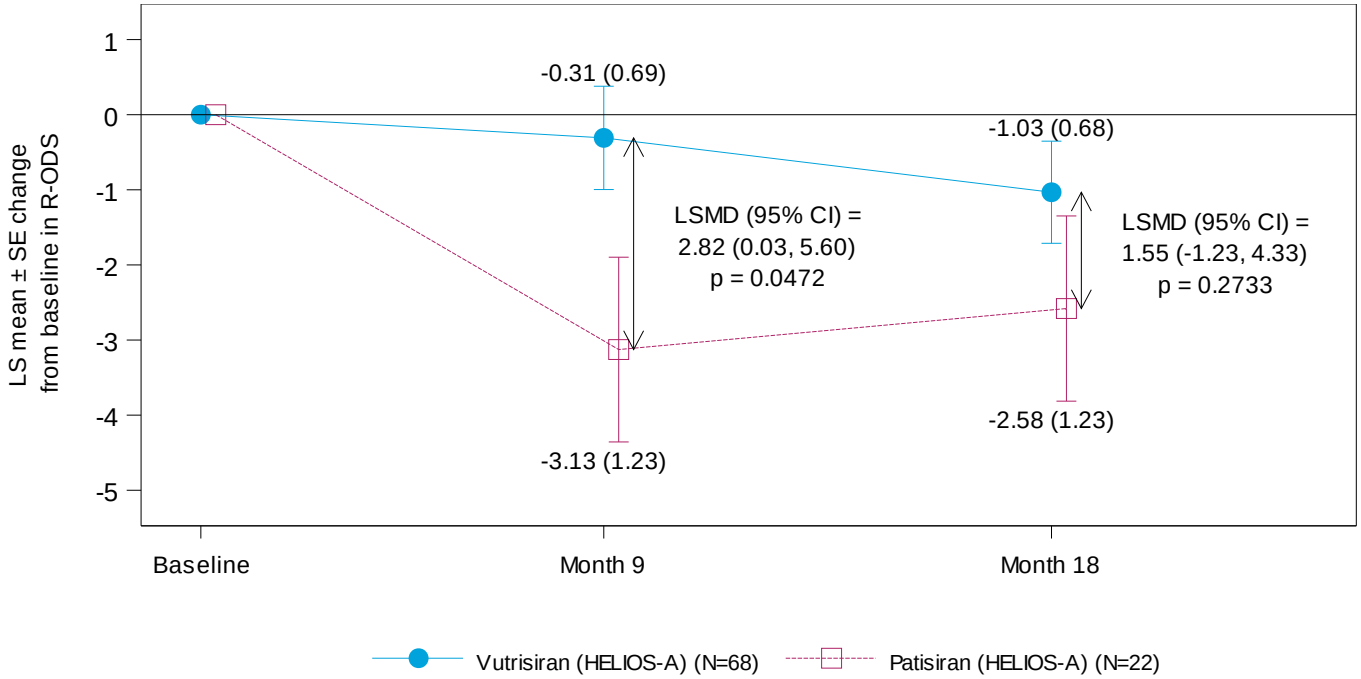
N evaluable			
Vutrisiran	54	51	52
Patisiran	20	20	20

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

Alnylam Pharmaceuticals Inc.
ALN-TTRSC02-002

Rasch-built Overall Disability Scale (R-ODS): Change from Baseline Over Time Series Plot
Subgroup Analysis: Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A)
mITT Population

Genotype: non-V30M



N evaluable			
Vutrisiran	68	64	62
Patisiran	22	20	18

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

Alnylam Pharmaceuticals Inc.
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Table 6.2
Rasch-built Overall Disability Scale (R-ODS): Change from Baseline to Month 18, MMRM Model
Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A) Subgroup Analysis
mITT Population

Subgroup Visit	LS Mean (95% CI) Vutrisiran (HELIOS-A) (N=122)	LS Mean (95% CI) Patisiran (HELIOS-A) (N=42)	LS Mean Difference (Vutrisiran-Patisiran) (95% CI), p-value	Standardized Effect Size (95% CI)
FAP Stage				
I	83	30		
Month 9	0.64 (-0.64, 1.92)	-0.44 (-2.49, 1.62)	1.08 (-1.27, 3.43), 0.3659	0.19 (-0.23, 0.60)
Month 18	-0.08 (-1.32, 1.16)	0.08 (-1.88, 2.04)	-0.16 (-2.40, 2.08), 0.8900	-0.03 (-0.45, 0.38)
II&III	35	10		
Month 9	-2.82 (-4.80, -0.83)	-5.68 (-9.10, -2.26)	2.87 (-0.87, 6.60), 0.1315	0.49 (-0.21, 1.19)
Month 18	-3.54 (-5.49, -1.58)	-5.17 (-8.59, -1.74)	1.63 (-2.09, 5.35), 0.3890	0.24 (-0.52, 1.00)
p-value of Treatment*FAP Stage	0.4009			

R-ODS score = composite of 24 disability questions; higher scores indicate lower disability (range = 0 to 48). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.
LS estimates and p-value derived from mixed-effects model for repeated measures (MMRM), controlling for categorical factors (treatment, visit), the subgroup variable, continuous covariate (baseline value), and interaction (treatment by visit, treatment by subgroup).
Standardized effect size (d) = LS mean difference/estimated pooled standard deviation with the small sample bias correction.

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

Alnylam Pharmaceuticals Inc.
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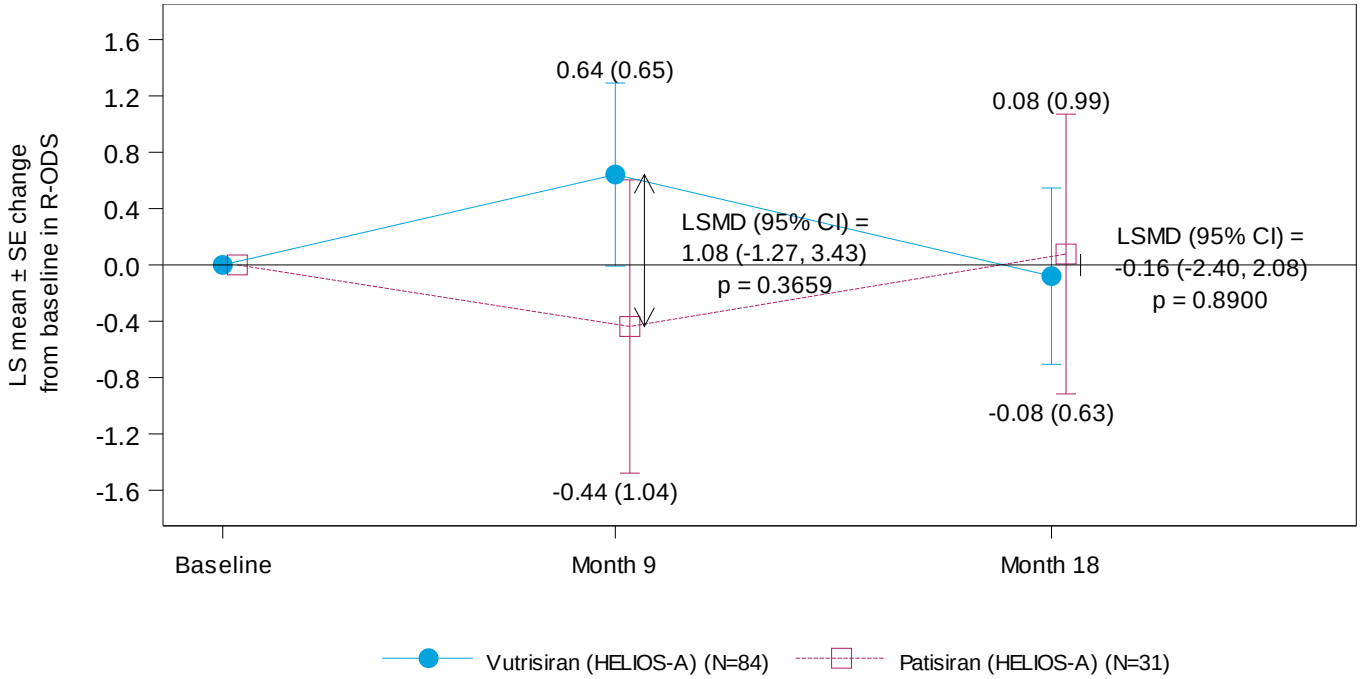
Rasch-built Overall Disability Scale (R-ODS): Change from Baseline Over Time Series Plot
Subgroup Analysis: Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A)
mITT Population

FAP Stage: I



N evaluable			
Vutrisiran	84	82	81
Patisiran	31	30	30

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

Alnylam Pharmaceuticals Inc.
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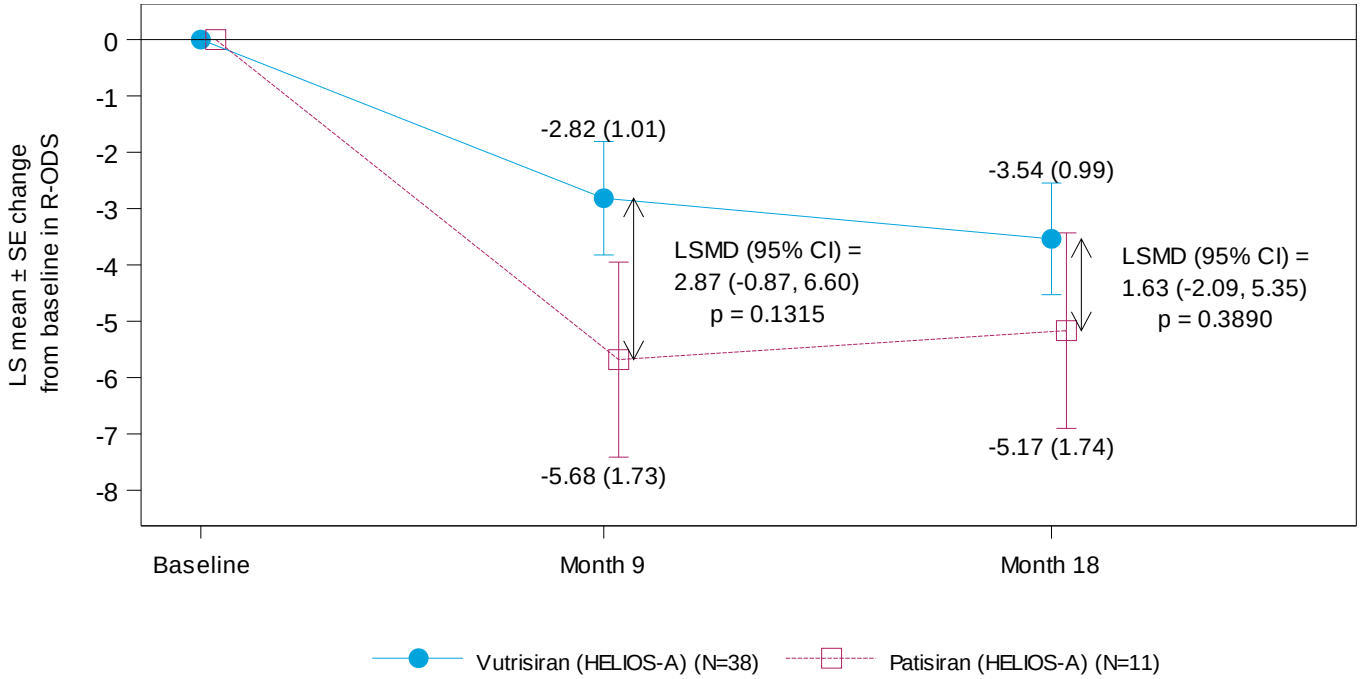
Rasch-built Overall Disability Scale (R-ODS): Change from Baseline Over Time Series Plot
Subgroup Analysis: Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A)
mITT Population

FAP Stage: II&III



N evaluable			
Vutrisiran	38	33	33
Patisiran	11	10	8

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

Alnylam Pharmaceuticals Inc.
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Table 6.2
Rasch-built Overall Disability Scale (R-ODS): Change from Baseline to Month 18, MMRM Model
Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A) Subgroup Analysis
mITT Population

Subgroup Visit	LS Mean (95% CI) Vutrisiran (HELIOS-A) (N=122)	LS Mean (95% CI) Patisiran (HELIOS-A) (N=42)	LS Mean Difference (Vutrisiran-Patisiran) (95% CI), p-value	Standardized Effect Size (95% CI)
Cardiac Subpopulation				
Yes	38	14		
Month 9	-0.58 (-2.34, 1.18)	-3.83 (-6.70, -0.95)	3.25 (-0.08, 6.58), 0.0560	0.44 (-0.17, 1.05)
Month 18	-1.30 (-3.05, 0.44)	-3.26 (-6.13, -0.39)	1.95 (-1.36, 5.27), 0.2459	0.31 (-0.32, 0.93)
No	80	26		
Month 9	-0.33 (-1.59, 0.93)	-0.72 (-2.91, 1.46)	0.40 (-2.10, 2.89), 0.7524	0.08 (-0.36, 0.52)
Month 18	-1.05 (-2.29, 0.19)	-0.16 (-2.32, 2.00)	-0.89 (-3.35, 1.57), 0.4745	-0.17 (-0.62, 0.28)
p-value of Treatment*Cardiac Subpopulation	0.1560			

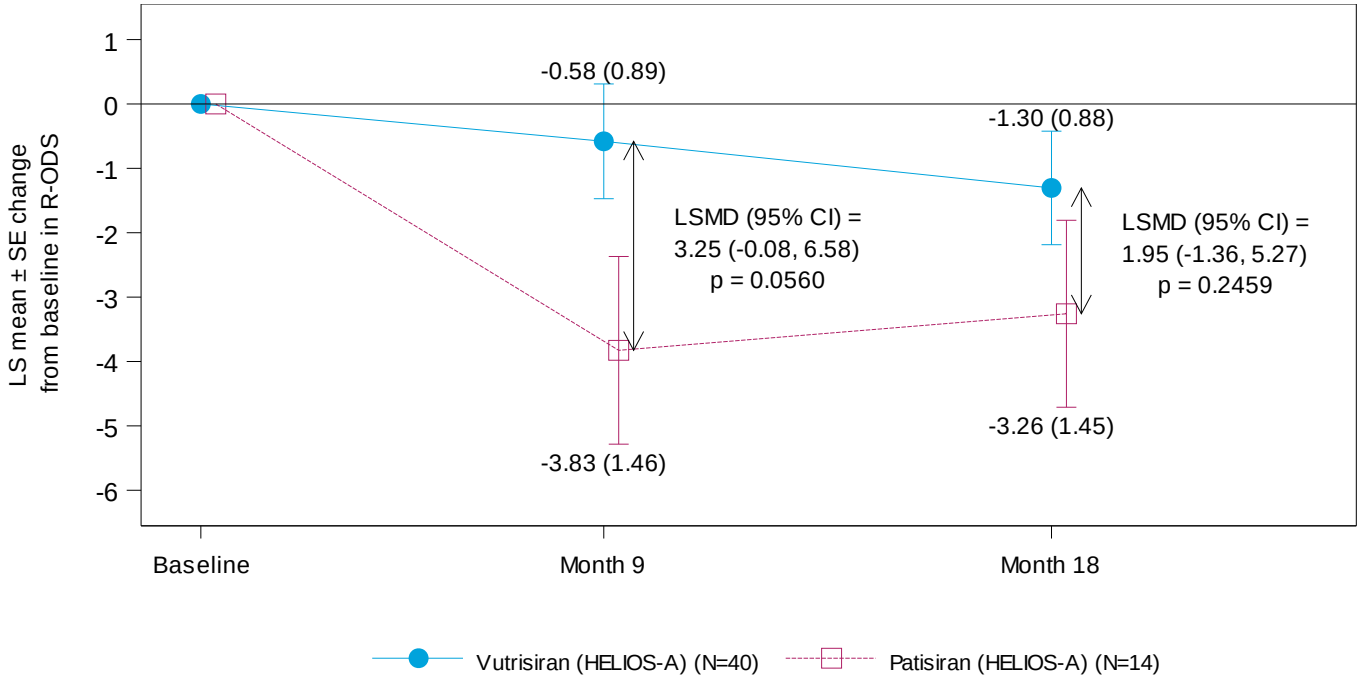
R-ODS score = composite of 24 disability questions; higher scores indicate lower disability (range = 0 to 48). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.
LS estimates and p-value derived from mixed-effects model for repeated measures (MMRM), controlling for categorical factors (treatment, visit), the subgroup variable, continuous covariate (baseline value), and interaction (treatment by visit, treatment by subgroup).
Standardized effect size (d) = LS mean difference/estimated pooled standard deviation with the small sample bias correction.

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

Alnylam Pharmaceuticals Inc.
ALN-TTRSC02-002

Rasch-built Overall Disability Scale (R-ODS): Change from Baseline Over Time Series Plot
Subgroup Analysis: Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A)
mITT Population

Cardiac Subpopulation: Yes



N evaluable			
Vutrisiran	40	37	37
Patisiran	14	14	13

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

Alnylam Pharmaceuticals Inc.
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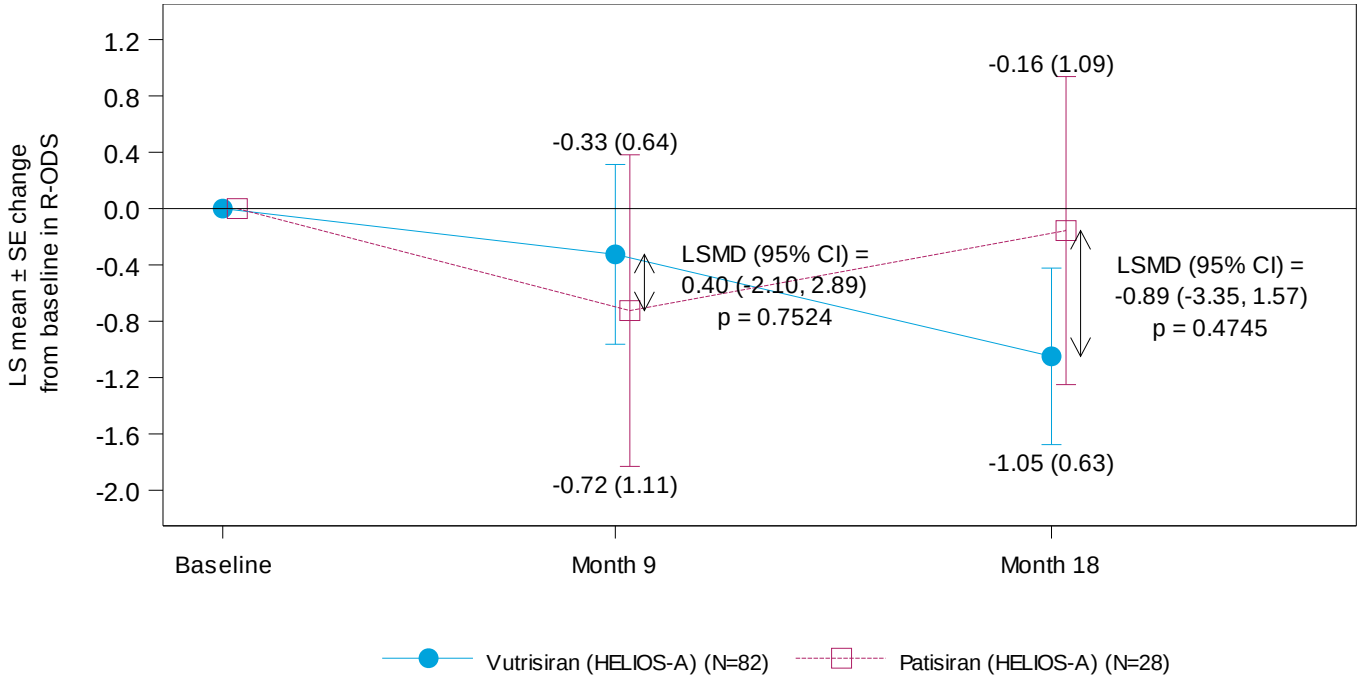
Rasch-built Overall Disability Scale (R-ODS): Change from Baseline Over Time Series Plot
Subgroup Analysis: Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A)
mITT Population

Cardiac Subpopulation: No



N evaluable			
Vutrisiran	82	78	77
Patisiran	28	26	25

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

Alnylam Pharmaceuticals Inc.
ALN-TTRSC02-002

Table 6.2
Rasch-built Overall Disability Scale (R-ODS): Change from Baseline to Month 18, MMRM Model
Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A) Subgroup Analysis
mITT Population

Subgroup Visit	LS Mean (95% CI) Vutrisiran (HELIOS-A) (N=122)	LS Mean (95% CI) Patisiran (HELIOS-A) (N=42)	LS Mean Difference (Vutrisiran-Patisiran) (95% CI), p-value	Standardized Effect Size (95% CI)
Weight (kg)				
<65	44	15		
Month 9	-0.86 (-2.48, 0.76)	-3.00 (-5.76, -0.24)	2.14 (-1.07, 5.35), 0.1891	0.35 (-0.23, 0.93)
Month 18	-1.59 (-3.20, 0.03)	-2.41 (-5.15, 0.33)	0.83 (-2.36, 4.01), 0.6096	0.13 (-0.45, 0.72)
≥65	74	25		
Month 9	-0.14 (-1.44, 1.15)	-1.11 (-3.31, 1.08)	0.97 (-1.58, 3.52), 0.4542	0.17 (-0.28, 0.63)
Month 18	-0.87 (-2.15, 0.40)	-0.53 (-2.73, 1.68)	-0.35 (-2.89, 2.20), 0.7875	-0.07 (-0.53, 0.40)
p-value of Treatment*Weight	0.5522			

R-ODS score = composite of 24 disability questions; higher scores indicate lower disability (range = 0 to 48). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.
LS estimates and p-value derived from mixed-effects model for repeated measures (MMRM), controlling for categorical factors (treatment, visit), the subgroup variable, continuous covariate (baseline value), and interaction (treatment by visit, treatment by subgroup).
Standardized effect size (d) = LS mean difference/estimated pooled standard deviation with the small sample bias correction.

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

Alnylam Pharmaceuticals Inc.
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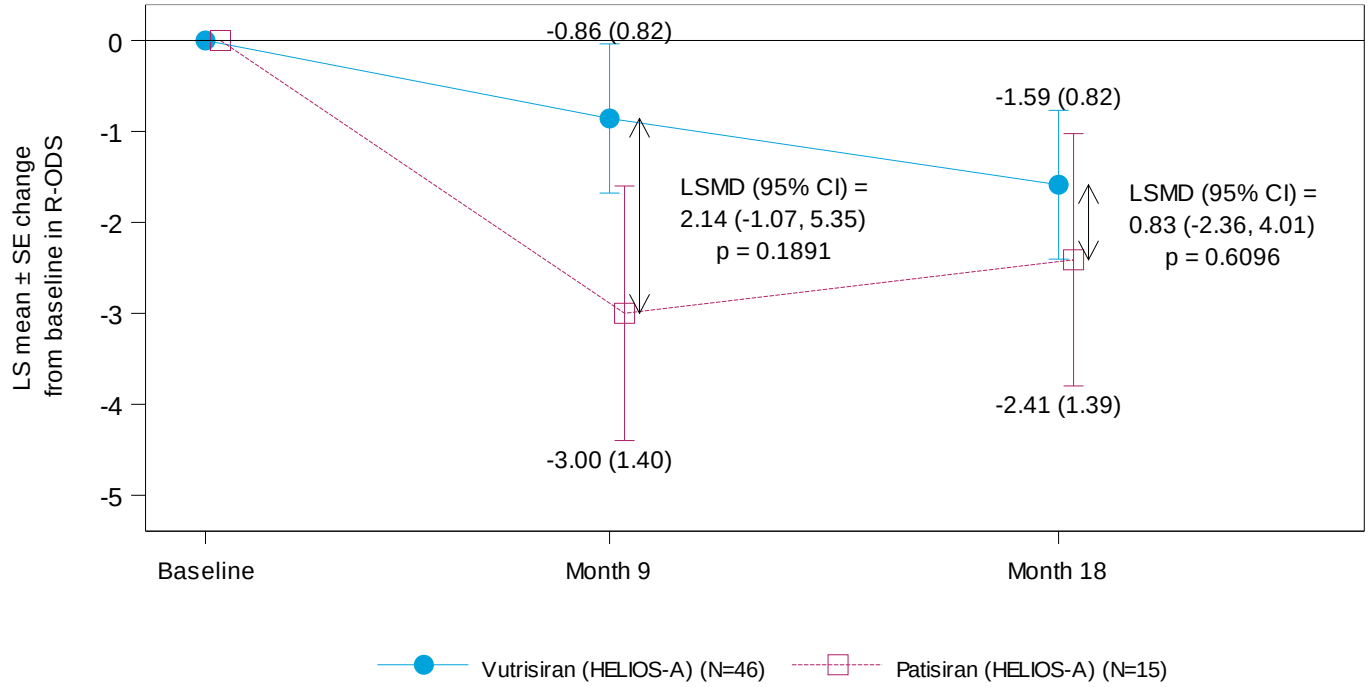
Rasch-built Overall Disability Scale (R-ODS): Change from Baseline Over Time Series Plot
Subgroup Analysis: Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A)
mITT Population

Weight (kg): <65



N evaluable

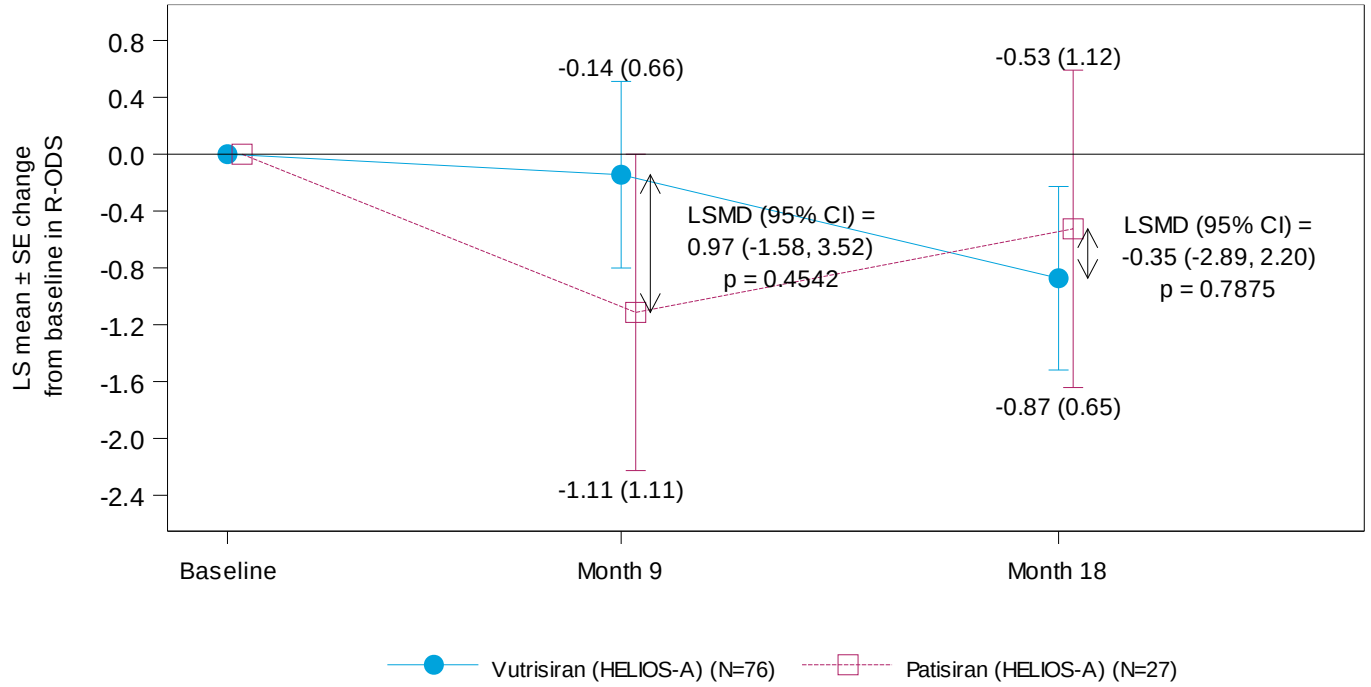
Vutrisiran	46	44	42
Patisiran	15	15	15

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

Alnylam Pharmaceuticals Inc.
ALN-TTRSC02-002

Rasch-built Overall Disability Scale (R-ODS): Change from Baseline Over Time Series Plot
Subgroup Analysis: Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A)
mITT Population

Weight (kg): ≥65



N evaluable			
Vutrisiran	76	71	72
Patisiran	27	25	23

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

Alnylam Pharmaceuticals Inc.
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Table 6.3
Rasch-built Overall Disability Scale (R-ODS): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Age (years): <65

Subgroup Visit	Vutrisiran (HELIOS-A) (N=76)	Patisiran (HELIOS-A) (N=31)
Baseline		
n	76	31
Mean (SD)	36.2 (9.9)	35.2 (10.1)
SE	1.1	1.8
Median	38.0	38.0
Min, Max	7, 48	9, 47
Month 9		
Actual Value		
n	74	30
Mean (SD)	35.1 (11.0)	34.0 (12.4)
SE	1.3	2.3
Median	37.0	36.5
Min, Max	8, 48	5, 48
Change from baseline		
n	74	30
Mean (SD)	-1.2 (4.8)	-1.9 (6.4)
SE	0.6	1.2
Median	0.0	-0.5
Min, Max	-18, 8	-21, 9

R-ODS score = composite of 24 disability questions; higher scores indicate lower disability (range = 0 to 48). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

Alnylam Pharmaceuticals Inc.
ALN-TTRSC02-002

Table 6.3
Rasch-built Overall Disability Scale (R-ODS): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Age (years): <65

Subgroup Visit	Vutrisiran (HELIOS-A) (N=76)	Patisiran (HELIOS-A) (N=31)
Month 18		
Actual Value		
n	74	29
Mean (SD)	35.1 (11.9)	35.5 (11.2)
SE	1.4	2.1
Median	37.0	36.0
Min, Max	5, 48	4, 48
Change from baseline		
n	74	29
Mean (SD)	-1.4 (5.7)	-1.3 (5.6)
SE	0.7	1.0
Median	0.0	0.0
Min, Max	-21, 13	-13, 8

R-ODS score = composite of 24 disability questions; higher scores indicate lower disability (range = 0 to 48). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

Alnylam Pharmaceuticals Inc.
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Table 6.3
Rasch-built Overall Disability Scale (R-ODS): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Age (years): ≥65

Subgroup Visit	Vutrisiran (HELIOS-A) (N=46)	Patisiran (HELIOS-A) (N=11)
Baseline		
n	46	11
Mean (SD)	30.5 (11.8)	30.8 (11.2)
SE	1.7	3.4
Median	33.5	30.0
Min, Max	5, 48	13, 47
Month 9		
Actual Value		
n	41	10
Mean (SD)	32.4 (12.9)	30.1 (12.6)
SE	2.0	4.0
Median	36.0	30.5
Min, Max	3, 48	12, 47
Change from baseline		
n	41	10
Mean (SD)	1.1 (6.5)	-1.6 (6.5)
SE	1.0	2.1
Median	0.0	-0.5
Min, Max	-11, 25	-16, 10

R-ODS score = composite of 24 disability questions; higher scores indicate lower disability (range = 0 to 48). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

Alnylam Pharmaceuticals Inc.
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Table 6.3
Rasch-built Overall Disability Scale (R-ODS): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Age (years): ≥65

Subgroup Visit	Vutrisiran (HELIOS-A) (N=46)	Patisiran (HELIOS-A) (N=11)
Month 18		
Actual Value		
n	40	9
Mean (SD)	30.4 (12.1)	30.2 (12.2)
SE	1.9	4.1
Median	31.5	32.0
Min, Max	3, 48	14, 46
Change from baseline		
n	40	9
Mean (SD)	-0.7 (5.2)	-1.0 (6.9)
SE	0.8	2.3
Median	0.0	-1.0
Min, Max	-13, 12	-18, 6

R-ODS score = composite of 24 disability questions; higher scores indicate lower disability (range = 0 to 48). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

Alnylam Pharmaceuticals Inc.
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Table 6.3
Rasch-built Overall Disability Scale (R-ODS): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Sex: Male

Subgroup Visit	Vutrisiran (HELIOS-A) (N=79)	Patisiran (HELIOS-A) (N=27)
Baseline		
n	79	27
Mean (SD)	34.3 (10.8)	33.6 (11.0)
SE	1.2	2.1
Median	37.0	34.0
Min, Max	6, 48	9, 47
Month 9		
Actual Value		
n	75	25
Mean (SD)	34.1 (12.0)	32.8 (12.2)
SE	1.4	2.4
Median	37.0	34.0
Min, Max	3, 48	5, 48
Change from baseline		
n	75	25
Mean (SD)	-0.5 (5.7)	-2.0 (6.0)
SE	0.7	1.2
Median	0.0	-1.0
Min, Max	-18, 25	-16, 10

R-ODS score = composite of 24 disability questions; higher scores indicate lower disability (range = 0 to 48). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

Alnylam Pharmaceuticals Inc.
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Table 6.3
Rasch-built Overall Disability Scale (R-ODS): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Sex: Male

Subgroup Visit	Vutrisiran (HELIOS-A) (N=79)	Patisiran (HELIOS-A) (N=27)
Month 18		
Actual Value		
n	74	23
Mean (SD)	33.0 (12.3)	34.7 (11.8)
SE	1.4	2.5
Median	36.5	35.0
Min, Max	3, 48	4, 48
Change from baseline		
n	74	23
Mean (SD)	-1.8 (5.8)	-1.1 (6.5)
SE	0.7	1.4
Median	-0.5	0.0
Min, Max	-21, 13	-18, 8

R-ODS score = composite of 24 disability questions; higher scores indicate lower disability (range = 0 to 48). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

Alnylam Pharmaceuticals Inc.
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Table 6.3
Rasch-built Overall Disability Scale (R-ODS): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Sex: Female

Subgroup Visit	Vutrisiran (HELIOS-A) (N=43)	Patisiran (HELIOS-A) (N=15)
Baseline		
n	43	15
Mean (SD)	33.8 (11.5)	34.9 (9.5)
SE	1.8	2.5
Median	35.0	35.0
Min, Max	5, 48	13, 47
Month 9		
Actual Value		
n	40	15
Mean (SD)	34.2 (11.4)	33.4 (13.2)
SE	1.8	3.4
Median	37.0	37.0
Min, Max	8, 48	6, 47
Change from baseline		
n	40	15
Mean (SD)	-0.3 (5.3)	-1.5 (7.0)
SE	0.8	1.8
Median	0.0	0.0
Min, Max	-15, 12	-21, 8

R-ODS score = composite of 24 disability questions; higher scores indicate lower disability (range = 0 to 48). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

Alnylam Pharmaceuticals Inc.
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Table 6.3
Rasch-built Overall Disability Scale (R-ODS): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Sex: Female

Subgroup Visit	Vutrisiran (HELIOS-A) (N=43)	Patisiran (HELIOS-A) (N=15)
Month 18		
Actual Value		
n	40	15
Mean (SD)	34.3 (12.0)	33.4 (11.4)
SE	1.9	2.9
Median	35.0	35.0
Min, Max	7, 48	14, 48
Change from baseline		
n	40	15
Mean (SD)	0.0 (5.0)	-1.4 (4.9)
SE	0.8	1.3
Median	0.0	0.0
Min, Max	-11, 12	-13, 3

R-ODS score = composite of 24 disability questions; higher scores indicate lower disability (range = 0 to 48). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

Alnylam Pharmaceuticals Inc.
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Table 6.3
Rasch-built Overall Disability Scale (R-ODS): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Race: White

Subgroup Visit	Vutrisiran (HELIOS-A) (N=86)	Patisiran (HELIOS-A) (N=29)
Baseline		
n	86	29
Mean (SD)	34.6 (11.4)	33.2 (10.2)
SE	1.2	1.9
Median	37.0	35.0
Min, Max	5, 48	9, 47
Month 9		
Actual Value		
n	81	28
Mean (SD)	34.7 (11.6)	31.6 (13.2)
SE	1.3	2.5
Median	37.0	35.0
Min, Max	3, 48	5, 47
Change from baseline		
n	81	28
Mean (SD)	-0.6 (4.6)	-1.9 (6.4)
SE	0.5	1.2
Median	0.0	-1.0
Min, Max	-15, 11	-21, 10

R-ODS score = composite of 24 disability questions; higher scores indicate lower disability (range = 0 to 48). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

Alnylam Pharmaceuticals Inc.
ALN-TTRSC02-002

Table 6.3
Rasch-built Overall Disability Scale (R-ODS): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Race: White

Subgroup Visit	Vutrisiran (HELIOS-A) (N=86)	Patisiran (HELIOS-A) (N=29)
Month 18		
Actual Value		
n	81	27
Mean (SD)	34.0 (12.3)	33.4 (11.9)
SE	1.4	2.3
Median	37.0	35.0
Min, Max	3, 48	4, 46
Change from baseline		
n	81	27
Mean (SD)	-1.3 (5.1)	-1.0 (5.3)
SE	0.6	1.0
Median	0.0	0.0
Min, Max	-15, 12	-13, 6

R-ODS score = composite of 24 disability questions; higher scores indicate lower disability (range = 0 to 48). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

Alnylam Pharmaceuticals Inc.
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Table 6.3
Rasch-built Overall Disability Scale (R-ODS): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Race: All Other Races

Subgroup Visit	Vutrisiran (HELIOS-A) (N=36)	Patisiran (HELIOS-A) (N=13)
Baseline		
n	36	13
Mean (SD)	32.8 (10.0)	35.9 (10.9)
SE	1.7	3.0
Median	34.0	36.0
Min, Max	7, 48	14, 47
Month 9		
Actual Value		
n	34	12
Mean (SD)	33.0 (12.0)	36.2 (10.2)
SE	2.1	2.9
Median	36.0	36.5
Min, Max	8, 48	17, 48
Change from baseline		
n	34	12
Mean (SD)	0.0 (7.4)	-1.6 (6.4)
SE	1.3	1.9
Median	0.0	0.0
Min, Max	-18, 25	-16, 9

R-ODS score = composite of 24 disability questions; higher scores indicate lower disability (range = 0 to 48). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

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Table 6.3
Rasch-built Overall Disability Scale (R-ODS): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Race: All Other Races

Subgroup Visit	Vutrisiran (HELIOS-A) (N=36)	Patisiran (HELIOS-A) (N=13)
Month 18		
Actual Value		
n	33	11
Mean (SD)	32.1 (11.9)	36.2 (10.7)
SE	2.1	3.2
Median	34.0	34.0
Min, Max	5, 48	15, 48
Change from baseline		
n	33	11
Mean (SD)	-0.8 (6.5)	-1.7 (7.3)
SE	1.1	2.2
Median	0.0	0.0
Min, Max	-21, 13	-18, 8

R-ODS score = composite of 24 disability questions; higher scores indicate lower disability (range = 0 to 48). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

Alnylam Pharmaceuticals Inc.
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Table 6.3
Rasch-built Overall Disability Scale (R-ODS): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Region: North America

Subgroup Visit	Vutrisiran (HELIOS-A) (N=27)	Patisiran (HELIOS-A) (N=8)
Baseline		
n	27	8
Mean (SD)	38.5 (7.7)	37.4 (4.3)
SE	1.5	1.5
Median	41.0	37.5
Min, Max	25, 48	31, 43
Month 9		
Actual Value		
n	25	8
Mean (SD)	39.3 (10.1)	33.8 (11.3)
SE	2.0	4.0
Median	44.0	35.5
Min, Max	16, 48	17, 46
Change from baseline		
n	25	8
Mean (SD)	-0.1 (5.6)	-3.6 (7.3)
SE	1.1	2.6
Median	0.0	-2.0
Min, Max	-15, 12	-16, 4

R-ODS score = composite of 24 disability questions; higher scores indicate lower disability (range = 0 to 48). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

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Table 6.3
Rasch-built Overall Disability Scale (R-ODS): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Region: North America

Subgroup Visit	Vutrisiran (HELIOS-A) (N=27)	Patisiran (HELIOS-A) (N=8)
Month 18		
Actual Value		
n	25	7
Mean (SD)	39.1 (9.4)	34.9 (12.5)
SE	1.9	4.7
Median	42.0	41.0
Min, Max	18, 48	15, 46
Change from baseline		
n	25	7
Mean (SD)	0.3 (5.7)	-2.7 (8.5)
SE	1.1	3.2
Median	1.0	0.0
Min, Max	-11, 13	-18, 5

R-ODS score = composite of 24 disability questions; higher scores indicate lower disability (range = 0 to 48). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

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Table 6.3
Rasch-built Overall Disability Scale (R-ODS): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Region: Western Europe

Subgroup Visit	Vutrisiran (HELIOS-A) (N=42)	Patisiran (HELIOS-A) (N=20)
Baseline		
n	42	20
Mean (SD)	35.0 (11.1)	33.3 (10.5)
SE	1.7	2.3
Median	37.5	33.5
Min, Max	5, 48	13, 47
Month 9		
Actual Value		
n	38	18
Mean (SD)	34.7 (10.9)	34.9 (10.1)
SE	1.8	2.4
Median	37.0	36.5
Min, Max	12, 48	12, 47
Change from baseline		
n	38	18
Mean (SD)	-1.4 (4.7)	0.0 (4.7)
SE	0.8	1.1
Median	-1.0	-0.5
Min, Max	-12, 10	-12, 10

R-ODS score = composite of 24 disability questions; higher scores indicate lower disability (range = 0 to 48). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

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Table 6.3
Rasch-built Overall Disability Scale (R-ODS): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Region: Western Europe

Subgroup Visit	Vutrisiran (HELIOS-A) (N=42)	Patisiran (HELIOS-A) (N=20)
Month 18		
Actual Value		
n	39	18
Mean (SD)	34.9 (10.4)	35.8 (8.9)
SE	1.7	2.1
Median	37.0	35.5
Min, Max	14, 48	14, 46
Change from baseline		
n	39	18
Mean (SD)	-1.3 (5.3)	0.9 (2.1)
SE	0.9	0.5
Median	0.0	0.5
Min, Max	-15, 12	-2, 6

R-ODS score = composite of 24 disability questions; higher scores indicate lower disability (range = 0 to 48). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 6.3
Rasch-built Overall Disability Scale (R-ODS): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Region: Rest of World

Subgroup Visit	Vutrisiran (HELIOS-A) (N=53)	Patisiran (HELIOS-A) (N=14)
Baseline		
n	53	14
Mean (SD)	31.1 (11.6)	33.2 (12.8)
SE	1.6	3.4
Median	32.0	32.5
Min, Max	6, 48	9, 47
Month 9		
Actual Value		
n	52	14
Mean (SD)	31.3 (12.3)	30.1 (15.6)
SE	1.7	4.2
Median	32.5	34.0
Min, Max	3, 48	5, 48
Change from baseline		
n	52	14
Mean (SD)	0.2 (6.1)	-3.1 (7.3)
SE	0.8	2.0
Median	0.0	-0.5
Min, Max	-18, 25	-21, 9

R-ODS score = composite of 24 disability questions; higher scores indicate lower disability (range = 0 to 48). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

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Table 6.3
Rasch-built Overall Disability Scale (R-ODS): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Region: Rest of World

Subgroup Visit	Vutrisiran (HELIOS-A) (N=53)	Patisiran (HELIOS-A) (N=14)
Month 18		
Actual Value		
n	50	13
Mean (SD)	29.4 (13.4)	31.7 (14.4)
SE	1.9	4.0
Median	31.0	34.0
Min, Max	3, 48	4, 48
Change from baseline		
n	50	13
Mean (SD)	-1.8 (5.6)	-3.4 (7.1)
SE	0.8	2.0
Median	-1.0	0.0
Min, Max	-21, 12	-13, 8

R-ODS score = composite of 24 disability questions; higher scores indicate lower disability (range = 0 to 48). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 6.3
Rasch-built Overall Disability Scale (R-ODS): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Baseline NIS: <50

Subgroup Visit	Vutrisiran (HELIOS-A) (N=78)	Patisiran (HELIOS-A) (N=27)
Baseline		
n	78	27
Mean (SD)	39.7 (7.1)	39.3 (6.4)
SE	0.8	1.2
Median	41.0	40.0
Min, Max	18, 48	25, 47
Month 9		
Actual Value		
n	77	27
Mean (SD)	39.5 (8.1)	38.4 (8.4)
SE	0.9	1.6
Median	42.0	40.0
Min, Max	16, 48	17, 48
Change from baseline		
n	77	27
Mean (SD)	-0.3 (5.3)	-0.9 (6.1)
SE	0.6	1.2
Median	0.0	0.0
Min, Max	-15, 25	-16, 10

R-ODS score = composite of 24 disability questions; higher scores indicate lower disability (range = 0 to 48). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 6.3
Rasch-built Overall Disability Scale (R-ODS): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Baseline NIS: <50

Subgroup Visit	Vutrisiran (HELIOS-A) (N=78)	Patisiran (HELIOS-A) (N=27)
Month 18		
Actual Value		
n	75	26
Mean (SD)	39.6 (8.0)	38.9 (8.4)
SE	0.9	1.6
Median	41.0	41.5
Min, Max	18, 48	15, 48
Change from baseline		
n	75	26
Mean (SD)	-0.3 (5.0)	-0.5 (5.6)
SE	0.6	1.1
Median	0.0	0.5
Min, Max	-15, 13	-18, 8

R-ODS score = composite of 24 disability questions; higher scores indicate lower disability (range = 0 to 48). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

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Table 6.3
Rasch-built Overall Disability Scale (R-ODS): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Baseline NIS: ≥50

Subgroup Visit	Vutrisiran (HELIOS-A) (N=44)	Patisiran (HELIOS-A) (N=15)
Baseline		
n	44	15
Mean (SD)	24.1 (9.5)	24.6 (9.6)
SE	1.4	2.5
Median	24.0	25.0
Min, Max	5, 44	9, 45
Month 9		
Actual Value		
n	38	13
Mean (SD)	23.3 (10.4)	21.8 (12.1)
SE	1.7	3.4
Median	22.5	20.0
Min, Max	3, 43	5, 43
Change from baseline		
n	38	13
Mean (SD)	-0.6 (6.1)	-3.8 (6.6)
SE	1.0	1.8
Median	-0.5	-1.0
Min, Max	-18, 11	-21, 4

R-ODS score = composite of 24 disability questions; higher scores indicate lower disability (range = 0 to 48). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 6.3
Rasch-built Overall Disability Scale (R-ODS): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Baseline NIS: ≥50

Subgroup Visit	Vutrisiran (HELIOS-A) (N=44)	Patisiran (HELIOS-A) (N=15)
Month 18		
Actual Value		
n	39	12
Mean (SD)	21.5 (9.5)	24.2 (11.2)
SE	1.5	3.2
Median	21.0	23.0
Min, Max	3, 41	4, 41
Change from baseline		
n	39	12
Mean (SD)	-2.9 (6.2)	-2.8 (6.2)
SE	1.0	1.8
Median	-3.0	0.0
Min, Max	-21, 12	-13, 4

R-ODS score = composite of 24 disability questions; higher scores indicate lower disability (range = 0 to 48). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

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Table 6.3
Rasch-built Overall Disability Scale (R-ODS): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Previous Tetramer Stabilizer Use: Yes

Subgroup Visit	Vutrisiran (HELIOS-A) (N=75)	Patisiran (HELIOS-A) (N=33)
Baseline		
n	75	33
Mean (SD)	34.3 (11.1)	33.2 (11.0)
SE	1.3	1.9
Median	37.0	34.0
Min, Max	5, 48	9, 47
Month 9		
Actual Value		
n	73	32
Mean (SD)	34.0 (11.1)	32.8 (12.8)
SE	1.3	2.3
Median	36.0	36.0
Min, Max	8, 48	5, 48
Change from baseline		
n	73	32
Mean (SD)	-0.6 (5.7)	-1.1 (6.0)
SE	0.7	1.1
Median	0.0	0.0
Min, Max	-18, 25	-21, 10

R-ODS score = composite of 24 disability questions; higher scores indicate lower disability (range = 0 to 48). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

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Table 6.3
Rasch-built Overall Disability Scale (R-ODS): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Previous Tetramer Stabilizer Use: Yes

Subgroup Visit	Vutrisiran (HELIOS-A) (N=75)	Patisiran (HELIOS-A) (N=33)
Month 18		
Actual Value		
n	71	31
Mean (SD)	33.2 (12.2)	34.4 (11.5)
SE	1.4	2.1
Median	36.0	35.0
Min, Max	5, 48	4, 48
Change from baseline		
n	71	31
Mean (SD)	-1.5 (5.6)	-0.2 (4.8)
SE	0.7	0.9
Median	0.0	0.0
Min, Max	-21, 12	-13, 8

R-ODS score = composite of 24 disability questions; higher scores indicate lower disability (range = 0 to 48). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 6.3
Rasch-built Overall Disability Scale (R-ODS): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Previous Tetramer Stabilizer Use: No

Subgroup Visit	Vutrisiran (HELIOS-A) (N=47)	Patisiran (HELIOS-A) (N=9)
Baseline		
n	47	9
Mean (SD)	33.7 (10.9)	36.9 (7.9)
SE	1.6	2.6
Median	34.0	36.0
Min, Max	6, 48	22, 47
Month 9		
Actual Value		
n	42	8
Mean (SD)	34.5 (12.8)	33.9 (11.2)
SE	2.0	4.0
Median	39.0	35.0
Min, Max	3, 48	17, 47
Change from baseline		
n	42	8
Mean (SD)	-0.1 (5.4)	-4.9 (7.1)
SE	0.8	2.5
Median	0.0	-3.0
Min, Max	-15, 12	-16, 4

R-ODS score = composite of 24 disability questions; higher scores indicate lower disability (range = 0 to 48). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 6.3
Rasch-built Overall Disability Scale (R-ODS): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Previous Tetramer Stabilizer Use: No

Subgroup Visit	Vutrisiran (HELIOS-A) (N=47)	Patisiran (HELIOS-A) (N=9)
Month 18		
Actual Value		
n	43	7
Mean (SD)	33.8 (12.2)	33.3 (12.5)
SE	1.9	4.7
Median	36.0	34.0
Min, Max	3, 48	15, 48
Change from baseline		
n	43	7
Mean (SD)	-0.6 (5.4)	-5.9 (8.2)
SE	0.8	3.1
Median	0.0	-5.0
Min, Max	-11, 13	-18, 5

R-ODS score = composite of 24 disability questions; higher scores indicate lower disability (range = 0 to 48). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 6.3
Rasch-built Overall Disability Scale (R-ODS): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Genotype: V30M

Subgroup Visit	Vutrisiran (HELIOS-A) (N=54)	Patisiran (HELIOS-A) (N=20)
Baseline		
n	54	20
Mean (SD)	35.2 (10.9)	34.4 (8.8)
SE	1.5	2.0
Median	37.5	34.5
Min, Max	7, 48	13, 47
Month 9		
Actual Value		
n	51	20
Mean (SD)	34.5 (11.8)	33.4 (9.9)
SE	1.7	2.2
Median	37.0	35.0
Min, Max	3, 48	12, 47
Change from baseline		
n	51	20
Mean (SD)	-1.1 (3.9)	-1.0 (4.9)
SE	0.5	1.1
Median	0.0	-0.5
Min, Max	-11, 8	-12, 10

R-ODS score = composite of 24 disability questions; higher scores indicate lower disability (range = 0 to 48). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 6.3
Rasch-built Overall Disability Scale (R-ODS): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Genotype: V30M

Subgroup Visit	Vutrisiran (HELIOS-A) (N=54)	Patisiran (HELIOS-A) (N=20)
Month 18		
Actual Value		
n	52	20
Mean (SD)	35.0 (11.7)	34.7 (9.2)
SE	1.6	2.1
Median	37.5	34.5
Min, Max	3, 48	14, 47
Change from baseline		
n	52	20
Mean (SD)	-0.7 (4.9)	0.4 (3.6)
SE	0.7	0.8
Median	0.0	1.0
Min, Max	-13, 13	-11, 6

R-ODS score = composite of 24 disability questions; higher scores indicate lower disability (range = 0 to 48). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 6.3
Rasch-built Overall Disability Scale (R-ODS): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Genotype: non-V30M

Subgroup Visit	Vutrisiran (HELIOS-A) (N=68)	Patisiran (HELIOS-A) (N=22)
Baseline		
n	68	22
Mean (SD)	33.2 (11.0)	33.7 (11.9)
SE	1.3	2.5
Median	35.0	35.5
Min, Max	5, 48	9, 47
Month 9		
Actual Value		
n	64	20
Mean (SD)	33.9 (11.7)	32.6 (14.7)
SE	1.5	3.3
Median	37.0	38.0
Min, Max	6, 48	5, 48
Change from baseline		
n	64	20
Mean (SD)	0.2 (6.6)	-2.7 (7.5)
SE	0.8	1.7
Median	0.0	-0.5
Min, Max	-18, 25	-21, 9

R-ODS score = composite of 24 disability questions; higher scores indicate lower disability (range = 0 to 48). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 6.3
Rasch-built Overall Disability Scale (R-ODS): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Genotype: non-V30M

Subgroup Visit	Vutrisiran (HELIOS-A) (N=68)	Patisiran (HELIOS-A) (N=22)
Month 18		
Actual Value		
n	62	18
Mean (SD)	32.1 (12.4)	33.7 (13.9)
SE	1.6	3.3
Median	35.0	38.0
Min, Max	5, 48	4, 48
Change from baseline		
n	62	18
Mean (SD)	-1.6 (6.0)	-3.1 (7.3)
SE	0.8	1.7
Median	-1.0	-0.5
Min, Max	-21, 12	-18, 8

R-ODS score = composite of 24 disability questions; higher scores indicate lower disability (range = 0 to 48). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 6.3
Rasch-built Overall Disability Scale (R-ODS): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

FAP Stage: I

Subgroup Visit	Vutrisiran (HELIOS-A) (N=84)	Patisiran (HELIOS-A) (N=31)
Baseline		
n	84	31
Mean (SD)	38.6 (8.2)	37.9 (7.7)
SE	0.9	1.4
Median	41.0	40.0
Min, Max	12, 48	22, 47
Month 9		
Actual Value		
n	82	30
Mean (SD)	38.5 (8.9)	37.3 (9.8)
SE	1.0	1.8
Median	41.0	40.0
Min, Max	15, 48	6, 48
Change from baseline		
n	82	30
Mean (SD)	-0.3 (5.5)	-1.1 (6.3)
SE	0.6	1.1
Median	0.0	0.0
Min, Max	-15, 25	-21, 10

R-ODS score = composite of 24 disability questions; higher scores indicate lower disability (range = 0 to 48). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

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Table 6.3
Rasch-built Overall Disability Scale (R-ODS): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

FAP Stage: I

Subgroup Visit	Vutrisiran (HELIOS-A) (N=84)	Patisiran (HELIOS-A) (N=31)
Month 18		
Actual Value		
n	81	30
Mean (SD)	38.5 (8.9)	38.1 (8.4)
SE	1.0	1.5
Median	40.0	40.5
Min, Max	13, 48	14, 48
Change from baseline		
n	81	30
Mean (SD)	-0.4 (4.8)	-0.3 (4.8)
SE	0.5	0.9
Median	0.0	0.0
Min, Max	-15, 13	-13, 8

R-ODS score = composite of 24 disability questions; higher scores indicate lower disability (range = 0 to 48). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

Alnylam Pharmaceuticals Inc.
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Table 6.3
Rasch-built Overall Disability Scale (R-ODS): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

FAP Stage: II&III

Subgroup Visit	Vutrisiran (HELIOS-A) (N=38)	Patisiran (HELIOS-A) (N=11)
Baseline		
n	38	11
Mean (SD)	24.1 (9.8)	23.2 (9.6)
SE	1.6	2.9
Median	23.0	22.0
Min, Max	5, 44	9, 36
Month 9		
Actual Value		
n	33	10
Mean (SD)	23.4 (11.0)	20.0 (10.2)
SE	1.9	3.2
Median	24.0	19.0
Min, Max	3, 46	5, 37
Change from baseline		
n	33	10
Mean (SD)	-0.6 (5.7)	-4.1 (6.2)
SE	1.0	2.0
Median	-1.0	-2.0
Min, Max	-18, 11	-16, 4

R-ODS score = composite of 24 disability questions; higher scores indicate lower disability (range = 0 to 48). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Alnylam Pharmaceuticals Inc.
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Table 6.3
Rasch-built Overall Disability Scale (R-ODS): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

FAP Stage: II&III

Subgroup Visit	Vutrisiran (HELIOS-A) (N=38)	Patisiran (HELIOS-A) (N=11)
Month 18		
Actual Value		
n	33	8
Mean (SD)	21.0 (9.9)	19.8 (10.2)
SE	1.7	3.6
Median	20.0	18.5
Min, Max	3, 42	4, 34
Change from baseline		
n	33	8
Mean (SD)	-3.1 (6.7)	-4.8 (8.2)
SE	1.2	2.9
Median	-3.0	0.0
Min, Max	-21, 12	-18, 3

R-ODS score = composite of 24 disability questions; higher scores indicate lower disability (range = 0 to 48). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

Alnylam Pharmaceuticals Inc.
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Table 6.3
Rasch-built Overall Disability Scale (R-ODS): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Cardiac Subpopulation: Yes

Subgroup Visit	Vutrisiran (HELIOS-A) (N=40)	Patisiran (HELIOS-A) (N=14)
Baseline		
n	40	14
Mean (SD)	29.9 (12.1)	28.8 (12.4)
SE	1.9	3.3
Median	33.0	26.5
Min, Max	6, 48	9, 47
Month 9		
Actual Value		
n	37	14
Mean (SD)	30.2 (13.5)	25.5 (15.5)
SE	2.2	4.1
Median	34.0	20.5
Min, Max	3, 48	5, 48
Change from baseline		
n	37	14
Mean (SD)	0.6 (6.9)	-3.3 (8.6)
SE	1.1	2.3
Median	0.0	-1.0
Min, Max	-18, 25	-21, 10

R-ODS score = composite of 24 disability questions; higher scores indicate lower disability (range = 0 to 48). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Alnylam Pharmaceuticals Inc.
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Table 6.3
Rasch-built Overall Disability Scale (R-ODS): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Cardiac Subpopulation: Yes

Subgroup Visit	Vutrisiran (HELIOS-A) (N=40)	Patisiran (HELIOS-A) (N=14)
Month 18		
Actual Value		
n	37	13
Mean (SD)	28.2 (14.0)	26.7 (14.3)
SE	2.3	4.0
Median	35.0	24.0
Min, Max	3, 48	4, 48
Change from baseline		
n	37	13
Mean (SD)	-1.9 (5.6)	-3.6 (7.9)
SE	0.9	2.2
Median	-1.0	-1.0
Min, Max	-21, 10	-18, 8

R-ODS score = composite of 24 disability questions; higher scores indicate lower disability (range = 0 to 48). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

Alnylam Pharmaceuticals Inc.
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Table 6.3
Rasch-built Overall Disability Scale (R-ODS): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Cardiac Subpopulation: No

Subgroup Visit	Vutrisiran (HELIOS-A) (N=82)	Patisiran (HELIOS-A) (N=28)
Baseline		
n	82	28
Mean (SD)	36.1 (9.8)	36.6 (8.3)
SE	1.1	1.6
Median	38.0	38.0
Min, Max	5, 48	14, 47
Month 9		
Actual Value		
n	78	26
Mean (SD)	36.0 (10.4)	37.0 (8.2)
SE	1.2	1.6
Median	37.0	37.5
Min, Max	14, 48	19, 47
Change from baseline		
n	78	26
Mean (SD)	-0.8 (4.8)	-1.1 (4.7)
SE	0.5	0.9
Median	0.0	0.0
Min, Max	-15, 12	-12, 8

R-ODS score = composite of 24 disability questions; higher scores indicate lower disability (range = 0 to 48). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 6.3
Rasch-built Overall Disability Scale (R-ODS): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Cardiac Subpopulation: No

Subgroup Visit	Vutrisiran (HELIOS-A) (N=82)	Patisiran (HELIOS-A) (N=28)
Month 18		
Actual Value		
n	77	25
Mean (SD)	36.0 (10.3)	38.1 (7.5)
SE	1.2	1.5
Median	37.0	40.0
Min, Max	16, 48	20, 48
Change from baseline		
n	77	25
Mean (SD)	-0.8 (5.5)	0.0 (4.1)
SE	0.6	0.8
Median	0.0	1.0
Min, Max	-15, 13	-12, 5

R-ODS score = composite of 24 disability questions; higher scores indicate lower disability (range = 0 to 48). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

Alnylam Pharmaceuticals Inc.
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Table 6.3
Rasch-built Overall Disability Scale (R-ODS): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Weight (kg): <65

Subgroup Visit	Vutrisiran (HELIOS-A) (N=46)	Patisiran (HELIOS-A) (N=15)
Baseline		
n	46	15
Mean (SD)	32.1 (11.2)	35.5 (8.7)
SE	1.7	2.3
Median	32.5	35.0
Min, Max	6, 48	13, 47
Month 9		
Actual Value		
n	44	15
Mean (SD)	31.2 (12.0)	32.7 (12.2)
SE	1.8	3.1
Median	33.0	36.0
Min, Max	6, 48	6, 47
Change from baseline		
n	44	15
Mean (SD)	-1.1 (5.7)	-2.8 (7.1)
SE	0.9	1.8
Median	0.0	-2.0
Min, Max	-18, 11	-21, 8

R-ODS score = composite of 24 disability questions; higher scores indicate lower disability (range = 0 to 48). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 6.3
Rasch-built Overall Disability Scale (R-ODS): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Weight (kg): <65

Subgroup Visit	Vutrisiran (HELIOS-A) (N=46)	Patisiran (HELIOS-A) (N=15)
Month 18		
Actual Value		
n	42	15
Mean (SD)	31.4 (12.4)	32.9 (10.1)
SE	1.9	2.6
Median	32.5	34.0
Min, Max	5, 48	14, 47
Change from baseline		
n	42	15
Mean (SD)	-1.2 (6.4)	-2.6 (5.3)
SE	1.0	1.4
Median	0.0	0.0
Min, Max	-21, 13	-13, 3

R-ODS score = composite of 24 disability questions; higher scores indicate lower disability (range = 0 to 48). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 6.3
Rasch-built Overall Disability Scale (R-ODS): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Weight (kg): ≥65

Subgroup Visit	Vutrisiran (HELIOS-A) (N=76)	Patisiran (HELIOS-A) (N=27)
Baseline		
n	76	27
Mean (SD)	35.3 (10.7)	33.2 (11.3)
SE	1.2	2.2
Median	38.5	36.0
Min, Max	5, 48	9, 47
Month 9		
Actual Value		
n	71	25
Mean (SD)	36.0 (11.2)	33.2 (12.8)
SE	1.3	2.6
Median	38.0	36.0
Min, Max	3, 48	5, 48
Change from baseline		
n	71	25
Mean (SD)	0.1 (5.5)	-1.2 (5.9)
SE	0.6	1.2
Median	0.0	0.0
Min, Max	-10, 25	-16, 10

R-ODS score = composite of 24 disability questions; higher scores indicate lower disability (range = 0 to 48). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 6.3
Rasch-built Overall Disability Scale (R-ODS): Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Weight (kg): ≥65

Subgroup Visit	Vutrisiran (HELIOS-A) (N=76)	Patisiran (HELIOS-A) (N=27)
Month 18		
Actual Value		
n	72	23
Mean (SD)	34.6 (11.9)	35.1 (12.5)
SE	1.4	2.6
Median	37.5	40.0
Min, Max	3, 48	4, 48
Change from baseline		
n	72	23
Mean (SD)	-1.1 (5.0)	-0.3 (6.1)
SE	0.6	1.3
Median	0.0	1.0
Min, Max	-15, 11	-18, 8

R-ODS score = composite of 24 disability questions; higher scores indicate lower disability (range = 0 to 48). Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Subgruppenanalysen zum Endpunkt „Hospitalisierungen“

Hospitalisierung jeglicher Ursache

Alnylam Pharmaceuticals Inc.
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Table 17.2
Summary of All Cause and Cardiovascular Related Hospitalizations during the 18 Month Treatment Period
Subgroup Analysis
Safety Population

All-Cause Hospitalizations

Subgroup Statistics	Vutrisiran (HELIOS-A) (N=122) n (%)	Patisiran (HELIOS-A) (N=42) n (%)
Age (years)		
<65, n/N1 (%)	15/ 76 (19.7)	13/ 31 (41.9)
Risk difference (Vutrisiran - Patisiran), (95% CI)	-22.199 (-41.739, -2.659)	
Odds ratio (Vutrisiran/Patisiran), (95% CI)	0.340 (0.137, 0.846)	
Relative risk (Vutrisiran/Patisiran), (95% CI)	0.471 (0.255, 0.870)	
P-value [1]	0.0162	
≥65, n/N1 (%)	16/ 46 (34.8)	4/ 11 (36.4)
Risk difference (Vutrisiran - Patisiran), (95% CI)	-1.581 (-33.165, 30.003)	
Odds ratio (Vutrisiran/Patisiran), (95% CI)	0.933 (0.237, 3.674)	
Relative risk (Vutrisiran/Patisiran), (95% CI)	0.957 (0.398, 2.297)	
P-value [1]	0.9208	
P-value of Treatment*Age [2]	0.2507	

CV = cardiovascular.
Unstratified relative risk (RR), odds ratio (OR), and risk difference (RD) were presented. In estimation of the OR and RR, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the RD.
[1] p-value based on the Wald test testing whether the relative risk equals to 1.
[2] p-value from a logistic regression using the penalized likelihood estimation (the FIRTH option) and with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Alnylam Pharmaceuticals Inc.
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Table 17.2
Summary of All Cause and Cardiovascular Related Hospitalizations during the 18 Month Treatment Period
Subgroup Analysis
Safety Population

All-Cause Hospitalizations

Subgroup Statistics	Vutrisiran (HELIOS-A) (N=122) n (%)	Patisiran (HELIOS-A) (N=42) n (%)
Sex		
Male, n/N1 (%)	19/ 79 (24.1)	8/ 27 (29.6)
Risk difference (Vutrisiran - Patisiran), (95% CI)	-5.579 (-25.213, 14.055)	
Odds ratio (Vutrisiran/Patisiran), (95% CI)	0.752 (0.284, 1.992)	
Relative risk (Vutrisiran/Patisiran), (95% CI)	0.812 (0.403, 1.636)	
P-value [1]	0.5597	
Female, n/N1 (%)	12/ 43 (27.9)	9/ 15 (60.0)
Risk difference (Vutrisiran - Patisiran), (95% CI)	-32.093 (-60.278, -3.908)	
Odds ratio (Vutrisiran/Patisiran), (95% CI)	0.258 (0.075, 0.882)	
Relative risk (Vutrisiran/Patisiran), (95% CI)	0.465 (0.247, 0.877)	
P-value [1]	0.0179	
P-value of Treatment*Sex [2]	0.2086	

CV = cardiovascular.
Unstratified relative risk (RR), odds ratio (OR), and risk difference (RD) were presented. In estimation of the OR and RR, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the RD.
[1] p-value based on the Wald test testing whether the relative risk equals to 1.
[2] p-value from a logistic regression using the penalized likelihood estimation (the FIRTH option) and with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Table 17.2
Summary of All Cause and Cardiovascular Related Hospitalizations during the 18 Month Treatment Period
Subgroup Analysis
Safety Population

All-Cause Hospitalizations

Subgroup Statistics	Vutrisiran (HELIOS-A) (N=122) n (%)	Patisiran (HELIOS-A) (N=42) n (%)
Race		
White, n/N1 (%)	23/ 86 (26.7)	11/ 29 (37.9)
Risk difference (Vutrisiran - Patisiran), (95% CI)	-11.187 (-31.171, 8.798)	
Odds ratio (Vutrisiran/Patisiran), (95% CI)	0.597 (0.246, 1.454)	
Relative risk (Vutrisiran/Patisiran), (95% CI)	0.705 (0.394, 1.262)	
P-value [1]	0.2395	
All Other Races, n/N1 (%)	8/ 36 (22.2)	6/ 13 (46.2)
Risk difference (Vutrisiran - Patisiran), (95% CI)	-23.932 (-54.243, 6.380)	
Odds ratio (Vutrisiran/Patisiran), (95% CI)	0.333 (0.087, 1.278)	
Relative risk (Vutrisiran/Patisiran), (95% CI)	0.481 (0.206, 1.124)	
P-value [1]	0.0910	
P-value of Treatment*Race [2]	0.5035	

CV = cardiovascular.
Unstratified relative risk (RR), odds ratio (OR), and risk difference (RD) were presented. In estimation of the OR and RR, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the RD.
[1] p-value based on the Wald test testing whether the relative risk equals to 1.
[2] p-value from a logistic regression using the penalized likelihood estimation (the FIRTH option) and with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Table 17.2
Summary of All Cause and Cardiovascular Related Hospitalizations during the 18 Month Treatment Period
Subgroup Analysis
Safety Population

All-Cause Hospitalizations

Subgroup Statistics	Vutrisiran (HELIOS-A) (N=122) n (%)	Patisiran (HELIOS-A) (N=42) n (%)
Region		
North America, n/N1 (%)	10/ 27 (37.0)	4/ 8 (50.0)
Risk difference (Vutrisiran - Patisiran), (95% CI)	-12.963 (-52.107, 26.181)	
Odds ratio (Vutrisiran/Patisiran), (95% CI)	0.588 (0.120, 2.887)	
Relative risk (Vutrisiran/Patisiran), (95% CI)	0.741 (0.317, 1.733)	
P-value [1]	0.4888	
Western Europe, n/N1 (%)	10/ 42 (23.8)	8/ 20 (40.0)
Risk difference (Vutrisiran - Patisiran), (95% CI)	-16.190 (-41.228, 8.847)	
Odds ratio (Vutrisiran/Patisiran), (95% CI)	0.469 (0.150, 1.469)	
Relative risk (Vutrisiran/Patisiran), (95% CI)	0.595 (0.278, 1.275)	
P-value [1]	0.1821	
Rest of World, n/N1 (%)	11/ 53 (20.8)	5/ 14 (35.7)
Risk difference (Vutrisiran - Patisiran), (95% CI)	-14.960 (-42.331, 12.412)	
Odds ratio (Vutrisiran/Patisiran), (95% CI)	0.471 (0.131, 1.694)	
Relative risk (Vutrisiran/Patisiran), (95% CI)	0.581 (0.242, 1.398)	
P-value [1]	0.2256	
P-value of Treatment*Region [2]	0.9660	

CV = cardiovascular.
Unstratified relative risk (RR), odds ratio (OR), and risk difference (RD) were presented. In estimation of the OR and RR, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the RD.
[1] p-value based on the Wald test testing whether the relative risk equals to 1.
[2] p-value from a logistic regression using the penalized likelihood estimation (the FIRTH option) and with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Table 17.2
Summary of All Cause and Cardiovascular Related Hospitalizations during the 18 Month Treatment Period
Subgroup Analysis
Safety Population

All-Cause Hospitalizations

Subgroup Statistics	Vutrisiran (HELIOS-A) (N=122) n (%)	Patisiran (HELIOS-A) (N=42) n (%)
Baseline NIS		
<50, n/N1 (%)	20/ 78 (25.6)	13/ 27 (48.1)
Risk difference (Vutrisiran - Patisiran), (95% CI)	-22.507 (-43.699, -1.315)	
Odds ratio (Vutrisiran/Patisiran), (95% CI)	0.371 (0.149, 0.923)	
Relative risk (Vutrisiran/Patisiran), (95% CI)	0.533 (0.309, 0.918)	
P-value [1]	0.0232	
≥50, n/N1 (%)	11/ 44 (25.0)	4/ 15 (26.7)
Risk difference (Vutrisiran - Patisiran), (95% CI)	-1.667 (-27.445, 24.111)	
Odds ratio (Vutrisiran/Patisiran), (95% CI)	0.917 (0.242, 3.474)	
Relative risk (Vutrisiran/Patisiran), (95% CI)	0.938 (0.351, 2.505)	
P-value [1]	0.8976	
P-value of Treatment*Baseline NIS [2]	0.2990	

CV = cardiovascular.
Unstratified relative risk (RR), odds ratio (OR), and risk difference (RD) were presented. In estimation of the OR and RR, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the RD.
[1] p-value based on the Wald test testing whether the relative risk equals to 1.
[2] p-value from a logistic regression using the penalized likelihood estimation (the FIRTH option) and with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Table 17.2
Summary of All Cause and Cardiovascular Related Hospitalizations during the 18 Month Treatment Period
Subgroup Analysis
Safety Population

All-Cause Hospitalizations

Subgroup Statistics	Vutrisiran (HELIOS-A) (N=122) n (%)	Patisiran (HELIOS-A) (N=42) n (%)
Previous Tetramer Stabilizer Use		
Yes, n/N1 (%)	16/ 75 (21.3)	14/ 33 (42.4)
Risk difference (Vutrisiran - Patisiran), (95% CI)	-21.091 (-40.334, -1.848)	
Odds ratio (Vutrisiran/Patisiran), (95% CI)	0.368 (0.152, 0.891)	
Relative risk (Vutrisiran/Patisiran), (95% CI)	0.503 (0.279, 0.906)	
P-value [1]	0.0221	
No, n/N1 (%)	15/ 47 (31.9)	3/ 9 (33.3)
Risk difference (Vutrisiran - Patisiran), (95% CI)	-1.418 (-34.976, 32.139)	
Odds ratio (Vutrisiran/Patisiran), (95% CI)	0.938 (0.206, 4.267)	
Relative risk (Vutrisiran/Patisiran), (95% CI)	0.957 (0.347, 2.639)	
P-value [1]	0.9330	
P-value of Treatment*Previous Tetramer Stabilizer Use [2]	0.3301	

CV = cardiovascular.
Unstratified relative risk (RR), odds ratio (OR), and risk difference (RD) were presented. In estimation of the OR and RR, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the RD.
[1] p-value based on the Wald test testing whether the relative risk equals to 1.
[2] p-value from a logistic regression using the penalized likelihood estimation (the FIRTH option) and with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Table 17.2
Summary of All Cause and Cardiovascular Related Hospitalizations during the 18 Month Treatment Period
Subgroup Analysis
Safety Population

All-Cause Hospitalizations

Subgroup Statistics	Vutrisiran (HELIOS-A) (N=122) n (%)	Patisiran (HELIOS-A) (N=42) n (%)
Genotype		
V30M, n/N1 (%)	10/ 54 (18.5)	7/ 20 (35.0)
Risk difference (Vutrisiran - Patisiran), (95% CI)	-16.481 (-39.812, 6.849)	
Odds ratio (Vutrisiran/Patisiran), (95% CI)	0.422 (0.134, 1.329)	
Relative risk (Vutrisiran/Patisiran), (95% CI)	0.529 (0.233, 1.199)	
P-value [1]	0.1274	
non-V30M, n/N1 (%)	21/ 68 (30.9)	10/ 22 (45.5)
Risk difference (Vutrisiran - Patisiran), (95% CI)	-14.572 (-38.099, 8.954)	
Odds ratio (Vutrisiran/Patisiran), (95% CI)	0.536 (0.200, 1.435)	
Relative risk (Vutrisiran/Patisiran), (95% CI)	0.679 (0.381, 1.213)	
P-value [1]	0.1912	
P-value of Treatment*Genotype [2]	0.7567	

CV = cardiovascular.
Unstratified relative risk (RR), odds ratio (OR), and risk difference (RD) were presented. In estimation of the OR and RR, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the RD.
[1] p-value based on the Wald test testing whether the relative risk equals to 1.
[2] p-value from a logistic regression using the penalized likelihood estimation (the FIRTH option) and with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

Alnylam Pharmaceuticals Inc.
ALN-TTRSC02-002

Table 17.2
Summary of All Cause and Cardiovascular Related Hospitalizations during the 18 Month Treatment Period
Subgroup Analysis
Safety Population

All-Cause Hospitalizations

Subgroup Statistics	Vutrisiran (HELIOS-A) (N=122) n (%)	Patisiran (HELIOS-A) (N=42) n (%)
FAP Stage		
I, n/N1 (%)	19/ 84 (22.6)	12/ 31 (38.7)
Risk difference (Vutrisiran - Patisiran), (95% CI)	-16.091 (-35.431, 3.250)	
Odds ratio (Vutrisiran/Patisiran), (95% CI)	0.463 (0.191, 1.122)	
Relative risk (Vutrisiran/Patisiran), (95% CI)	0.584 (0.323, 1.058)	
P-value [1]	0.0762	
II&III, n/N1 (%)	12/ 38 (31.6)	5/ 11 (45.5)
Risk difference (Vutrisiran - Patisiran), (95% CI)	-13.876 (-46.804, 19.053)	
Odds ratio (Vutrisiran/Patisiran), (95% CI)	0.554 (0.141, 2.179)	
Relative risk (Vutrisiran/Patisiran), (95% CI)	0.695 (0.313, 1.544)	
P-value [1]	0.3715	
P-value of Treatment*FAP Stage [2]	0.8259	

CV = cardiovascular.
Unstratified relative risk (RR), odds ratio (OR), and risk difference (RD) were presented. In estimation of the OR and RR, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the RD.
[1] p-value based on the Wald test testing whether the relative risk equals to 1.
[2] p-value from a logistic regression using the penalized likelihood estimation (the FIRTH option) and with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Alnylam Pharmaceuticals Inc.
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Table 17.2
Summary of All Cause and Cardiovascular Related Hospitalizations during the 18 Month Treatment Period
Subgroup Analysis
Safety Population

All-Cause Hospitalizations

Subgroup Statistics	Vutrisiran (HELIOS-A) (N=122) n (%)	Patisiran (HELIOS-A) (N=42) n (%)
Cardiac Subpopulation		
Yes, n/N1 (%)	11/ 40 (27.5)	5/ 14 (35.7)
Risk difference (Vutrisiran - Patisiran), (95% CI)	-8.214 (-36.875, 20.447)	
Odds ratio (Vutrisiran/Patisiran), (95% CI)	0.683 (0.187, 2.493)	
Relative risk (Vutrisiran/Patisiran), (95% CI)	0.770 (0.324, 1.828)	
P-value [1]	0.5534	
No, n/N1 (%)	20/ 82 (24.4)	12/ 28 (42.9)
Risk difference (Vutrisiran - Patisiran), (95% CI)	-18.467 (-39.019, 2.085)	
Odds ratio (Vutrisiran/Patisiran), (95% CI)	0.430 (0.174, 1.060)	
Relative risk (Vutrisiran/Patisiran), (95% CI)	0.569 (0.321, 1.009)	
P-value [1]	0.0538	
P-value of Treatment*Cardiac Subpopulation [2]	0.5818	

CV = cardiovascular.
Unstratified relative risk (RR), odds ratio (OR), and risk difference (RD) were presented. In estimation of the OR and RR, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the RD.
[1] p-value based on the Wald test testing whether the relative risk equals to 1.
[2] p-value from a logistic regression using the penalized likelihood estimation (the FIRTH option) and with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

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Table 17.2
Summary of All Cause and Cardiovascular Related Hospitalizations during the 18 Month Treatment Period
Subgroup Analysis
Safety Population

All-Cause Hospitalizations

Subgroup Statistics	Vutrisiran (HELIOS-A) (N=122) n (%)	Patisiran (HELIOS-A) (N=42) n (%)
Weight (kg)		
<65 kg, n/N1 (%)	9/ 46 (19.6)	9/ 15 (60.0)
Risk difference (Vutrisiran - Patisiran), (95% CI)	-40.435 (-67.749, -13.121)	
Odds ratio (Vutrisiran/Patisiran), (95% CI)	0.162 (0.046, 0.574)	
Relative risk (Vutrisiran/Patisiran), (95% CI)	0.326 (0.159, 0.668)	
P-value [1]	0.0022	
>=65 kg, n/N1 (%)	22/ 76 (28.9)	8/ 27 (29.6)
Risk difference (Vutrisiran - Patisiran), (95% CI)	-0.682 (-20.698, 19.333)	
Odds ratio (Vutrisiran/Patisiran), (95% CI)	0.968 (0.369, 2.536)	
Relative risk (Vutrisiran/Patisiran), (95% CI)	0.977 (0.495, 1.928)	
P-value [1]	0.9464	
P-value of Treatment*Weight [2]	0.0352	

CV = cardiovascular.
Unstratified relative risk (RR), odds ratio (OR), and risk difference (RD) were presented. In estimation of the OR and RR, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the RD.
[1] p-value based on the Wald test testing whether the relative risk equals to 1.
[2] p-value from a logistic regression using the penalized likelihood estimation (the FIRTH option) and with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

Hospitalisierung aufgrund kardiovaskulärer Ereignisse

Für diesen Endpunkt wurden für die Subgruppenmerkmale Alter, Geschlecht, Region, NIS zu Baseline, Vorherige Behandlung mit Tetramer-Stabilisatoren, FAP-Stadium und Kardiale Subpopulation weniger als zehn Ereignisse in den jeweiligen Subgruppenausprägungen berichtet. Daher werden, den Vorgaben des G-BA entsprechend, keine Subgruppenanalysen für diese Subgruppenmerkmale dargestellt.

Alnylam Pharmaceuticals Inc.
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Table 17.2
Summary of All Cause and Cardiovascular Related Hospitalizations during the 18 Month Treatment Period
Subgroup Analysis
Safety Population

CV Hospitalizations

Subgroup Statistics	Vutrisiran (HELIOS-A) (N=122) n (%)	Patisiran (HELIOS-A) (N=42) n (%)
Race		
White, n/N1 (%)	8/ 86 (9.3)	3/ 29 (10.3)
Risk difference (Vutrisiran - Patisiran), (95% CI)	-1.043 (-13.713, 11.628)	
Odds ratio (Vutrisiran/Patisiran), (95% CI)	0.889 (0.219, 3.602)	
Relative risk (Vutrisiran/Patisiran), (95% CI)	0.899 (0.255, 3.165)	
P-value [1]	0.8686	
All Other Races, n/N1 (%)	1/ 36 (2.8)	2/ 13 (15.4)
Risk difference (Vutrisiran - Patisiran), (95% CI)	-12.607 (-32.941, 7.728)	
Odds ratio (Vutrisiran/Patisiran), (95% CI)	0.157 (0.013, 1.903)	
Relative risk (Vutrisiran/Patisiran), (95% CI)	0.181 (0.018, 1.828)	
P-value [1]	0.1473	
P-value of Treatment*Race [2]	0.2703	

CV = cardiovascular.
Unstratified relative risk (RR), odds ratio (OR), and risk difference (RD) were presented. In estimation of the OR and RR, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the RD.
[1] p-value based on the Wald test testing whether the relative risk equals to 1.
[2] p-value from a logistic regression using the penalized likelihood estimation (the FIRTH option) and with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Table 17.2
Summary of All Cause and Cardiovascular Related Hospitalizations during the 18 Month Treatment Period
Subgroup Analysis
Safety Population

CV Hospitalizations

Subgroup Statistics	Vutrisiran (HELIOS-A) (N=122) n (%)	Patisiran (HELIOS-A) (N=42) n (%)
Genotype		
V30M, n/N1 (%)	3/ 54 (5.6)	0/ 20 (0)
Risk difference (Vutrisiran - Patisiran), (95% CI)	5.556 (-0.554, 11.665)	
Odds ratio (Vutrisiran/Patisiran), (95% CI)	2.786 (0.138, 56.363)	
Relative risk (Vutrisiran/Patisiran), (95% CI)	2.673 (0.144, 49.567)	
P-value [1]	0.5094	
non-V30M, n/N1 (%)	6/ 68 (8.8)	5/ 22 (22.7)
Risk difference (Vutrisiran - Patisiran), (95% CI)	-13.904 (-32.668, 4.861)	
Odds ratio (Vutrisiran/Patisiran), (95% CI)	0.329 (0.089, 1.210)	
Relative risk (Vutrisiran/Patisiran), (95% CI)	0.388 (0.131, 1.149)	
P-value [1]	0.0875	
P-value of Treatment*Genotype [2]	0.2096	

CV = cardiovascular.
Unstratified relative risk (RR), odds ratio (OR), and risk difference (RD) were presented. In estimation of the OR and RR, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the RD.
[1] p-value based on the Wald test testing whether the relative risk equals to 1.
[2] p-value from a logistic regression using the penalized likelihood estimation (the FIRTH option) and with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Alnylam Pharmaceuticals Inc.
ALN-TTRSC02-002

Table 17.2
Summary of All Cause and Cardiovascular Related Hospitalizations during the 18 Month Treatment Period
Subgroup Analysis
Safety Population

CV Hospitalizations

Subgroup Statistics	Vutrisiran (HELIOS-A) (N=122) n (%)	Patisiran (HELIOS-A) (N=42) n (%)
Weight (kg)		
<65 kg, n/N1 (%)	1/ 46 (2.2)	2/ 15 (13.3)
Risk difference (Vutrisiran - Patisiran), (95% CI)	-11.159 (-28.871, 6.552)	
Odds ratio (Vutrisiran/Patisiran), (95% CI)	0.144 (0.012, 1.722)	
Relative risk (Vutrisiran/Patisiran), (95% CI)	0.163 (0.016, 1.673)	
P-value [1]	0.1269	
>=65 kg, n/N1 (%)	8/ 76 (10.5)	3/ 27 (11.1)
Risk difference (Vutrisiran - Patisiran), (95% CI)	-0.585 (-14.301, 13.131)	
Odds ratio (Vutrisiran/Patisiran), (95% CI)	0.941 (0.231, 3.840)	
Relative risk (Vutrisiran/Patisiran), (95% CI)	0.947 (0.271, 3.314)	
P-value [1]	0.9326	
P-value of Treatment*Weight [2]	0.2217	

CV = cardiovascular.
Unstratified relative risk (RR), odds ratio (OR), and risk difference (RD) were presented. In estimation of the OR and RR, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the RD.
[1] p-value based on the Wald test testing whether the relative risk equals to 1.
[2] p-value from a logistic regression using the penalized likelihood estimation (the FIRTH option) and with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Subgruppenanalysen zum Endpunkt „Veränderung der gesundheitsbezogenen Lebensqualität gemessen anhand des Norfolk-QoL-DN“

Norfolk-QoL-DN-Gesamtwert (Kontinuierliche Analyse)

Alnylam Pharmaceuticals Inc.
ALN-TTRSC02-002

Table 3.3
Norfolk Quality of Life - Diabetic Neuropathy (QoL-DN) Total Score: Change from Baseline to Month 18, MMRM Model
Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A) Subgroup Analysis
mITT Population

Subgroup Visit	LS Mean (95% CI) Vutrisiran (HELIOS-A) (N=122)	LS Mean (95% CI) Patisiran (HELIOS-A) (N=42)	LS Mean Difference (Vutrisiran-Patisiran) (95% CI), p-value	Standardized Effect Size (95% CI)
Age (years)				
<65	74	30		
Month 9	-2.74 (-6.65, 1.17)	-1.63 (-7.77, 4.50)	-1.11 (-8.38, 6.16), 0.7635	-0.06 (-0.48, 0.36)
Month 18	-1.12 (-5.43, 3.19)	-2.07 (-8.99, 4.85)	0.95 (-7.19, 9.10), 0.8174	0.05 (-0.38, 0.47)
≥65	43	10		
Month 9	-7.09 (-12.19, -1.98)	2.03 (-8.50, 12.56)	-9.12 (-20.82, 2.58), 0.1258	-0.58 (-1.27, 0.11)
Month 18	-5.46 (-10.89, -0.04)	1.59 (-9.43, 12.61)	-7.06 (-19.34, 5.23), 0.2586	-0.38 (-1.09, 0.34)
p-value of Treatment*Age	0.2490			

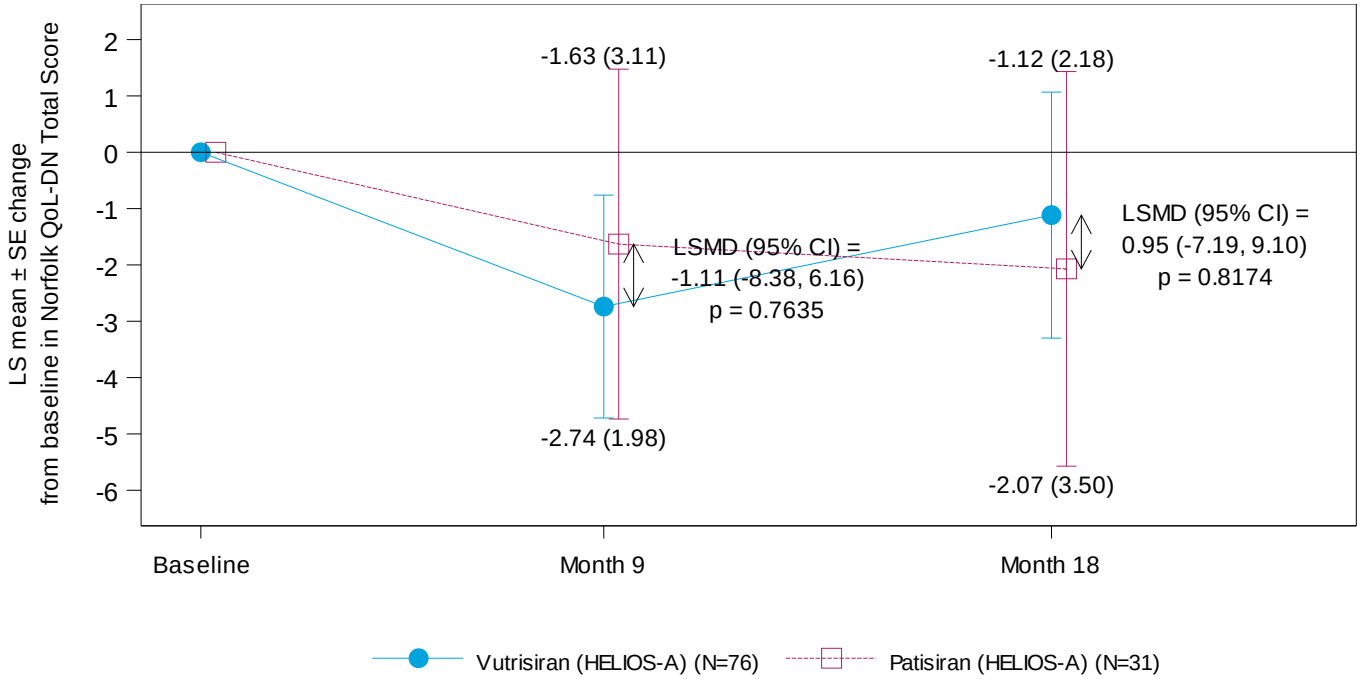
Norfolk QoL-DN score = composite of 35 quality of life questions; lower scores indicate higher quality of life (range = -4 to 136). Nonmissing scores for items 27-33 imputed for patients who reported an impact due to COVID-19 pandemic. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.
LS estimates and p-value derived from mixed-effects model for repeated measures (MMRM), controlling for categorical factors (treatment, visit), the subgroup variable, continuous covariate (baseline value), and interaction (treatment by visit, treatment by subgroup).
Standardized effect size (d) = LS mean difference/estimated pooled standard deviation with the small sample bias correction.

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

Alnylam Pharmaceuticals Inc.
ALN-TTRSC02-002

Norfolk Quality of Life - Diabetic Neuropathy (QoL-DN): Change from Baseline Over Time Series Plot
Subgroup Analysis: Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A)
mITT Population

Age (years): <65



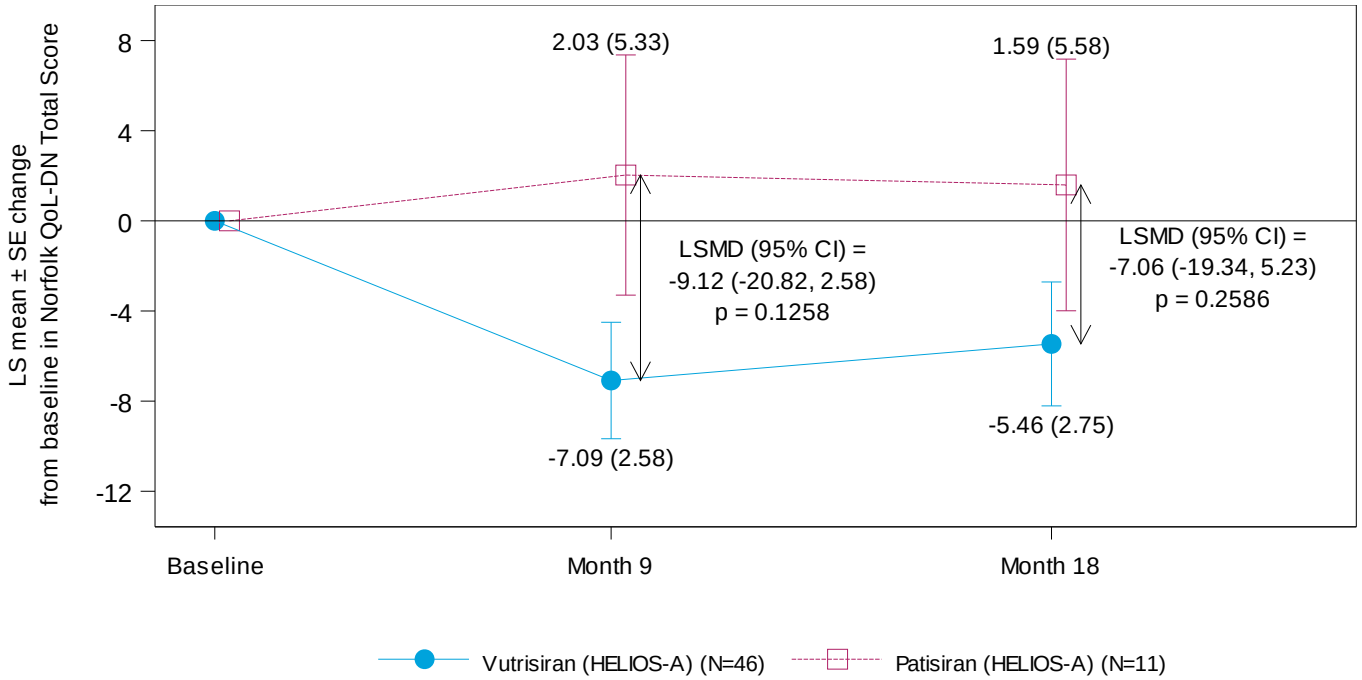
N evaluable			
Vutrisiran	75	73	73
Patisiran	31	30	29

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

Alnylam Pharmaceuticals Inc.
ALN-TTRSC02-002

Norfolk Quality of Life - Diabetic Neuropathy (QoL-DN): Change from Baseline Over Time Series Plot
Subgroup Analysis: Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A)
mITT Population

Age (years): ≥65



N evaluable			
Vutrisiran	46	42	40
Patisiran	11	10	9

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Table 3.3
Norfolk Quality of Life - Diabetic Neuropathy (QoL-DN) Total Score: Change from Baseline to Month 18, MMRM Model
Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A) Subgroup Analysis
mITT Population

Subgroup Visit	LS Mean (95% CI) Vutrisiran (HELIOS-A) (N=122)	LS Mean (95% CI) Patisiran (HELIOS-A) (N=42)	LS Mean Difference (Vutrisiran-Patisiran) (95% CI), p-value	Standardized Effect Size (95% CI)
Sex				
Male	76	25		
Month 9	-3.91 (-7.81, -0.02)	0.14 (-6.63, 6.91)	-4.05 (-11.86, 3.76), 0.3073	-0.22 (-0.67, 0.23)
Month 18	-2.28 (-6.53, 1.96)	-0.30 (-7.71, 7.11)	-1.98 (-10.52, 6.56), 0.6473	-0.09 (-0.56, 0.37)
Female	41	15		
Month 9	-5.11 (-10.38, 0.16)	-2.13 (-10.81, 6.54)	-2.98 (-13.13, 7.18), 0.5636	-0.21 (-0.80, 0.37)
Month 18	-3.48 (-9.01, 2.04)	-2.57 (-11.71, 6.56)	-0.91 (-11.59, 9.77), 0.8666	-0.06 (-0.64, 0.53)
p-value of Treatment*Sex	0.8672			

Norfolk QoL-DN score = composite of 35 quality of life questions; lower scores indicate higher quality of life (range = -4 to 136). Nonmissing scores for items 27-33 imputed for patients who reported an impact due to COVID-19 pandemic. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.
LS estimates and p-value derived from mixed-effects model for repeated measures (MMRM), controlling for categorical factors (treatment, visit), the subgroup variable, continuous covariate (baseline value), and interaction (treatment by visit, treatment by subgroup).
Standardized effect size (d) = LS mean difference/estimated pooled standard deviation with the small sample bias correction.

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Alnylam Pharmaceuticals Inc.
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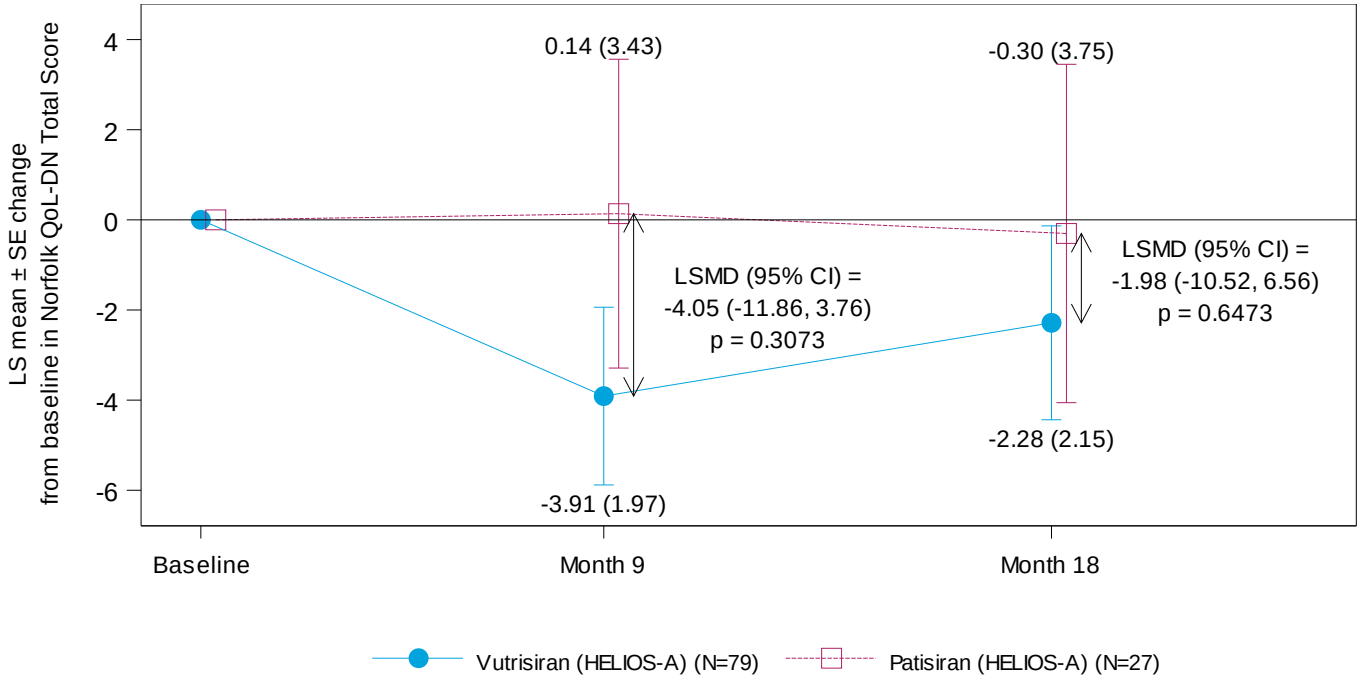
Norfolk Quality of Life - Diabetic Neuropathy (QoL-DN): Change from Baseline Over Time Series Plot
Subgroup Analysis: Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A)
mITT Population

Sex: Male



N evaluable			
Vutrisiran	78	75	73
Patisiran	27	25	23

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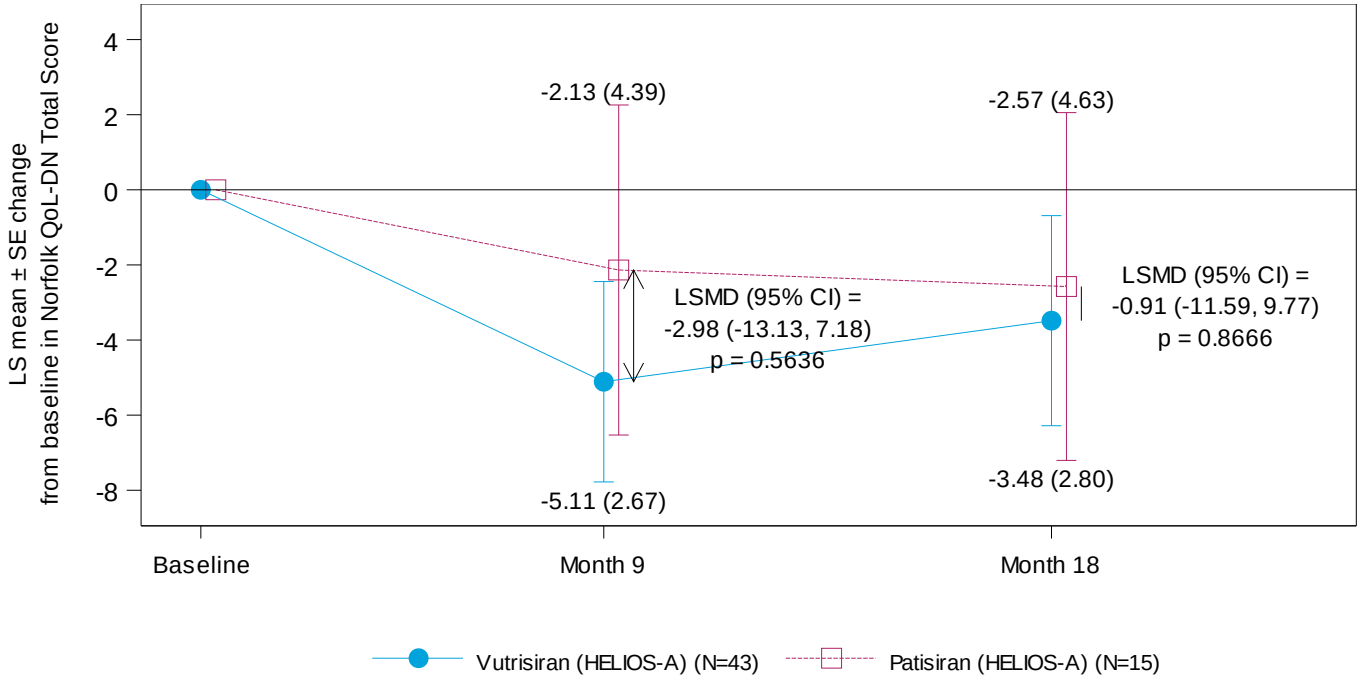
Alnylam Pharmaceuticals Inc.
ALN-TTRSC02-002

Norfolk Quality of Life - Diabetic Neuropathy (QoL-DN): Change from Baseline Over Time Series Plot
Subgroup Analysis: Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A)
mITT Population

Sex: Female



N evaluable			
Vutrisiran	43	40	40
Patisiran	15	15	15

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Alnylam Pharmaceuticals Inc.
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Table 3.3
Norfolk Quality of Life - Diabetic Neuropathy (QoL-DN) Total Score: Change from Baseline to Month 18, MMRM Model
Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A) Subgroup Analysis
mITT Population

Subgroup Visit	LS Mean (95% CI) Vutrisiran (HELIOS-A) (N=122)	LS Mean (95% CI) Patisiran (HELIOS-A) (N=42)	LS Mean Difference (Vutrisiran-Patisiran) (95% CI), p-value	Standardized Effect Size (95% CI)
Race				
White	82	28		
Month 9	-3.38 (-7.12, 0.36)	-1.04 (-7.44, 5.36)	-2.34 (-9.75, 5.07), 0.5337	-0.16 (-0.58, 0.27)
Month 18	-1.75 (-5.89, 2.38)	-1.49 (-8.58, 5.61)	-0.27 (-8.48, 7.95), 0.9487	-0.01 (-0.45, 0.42)
All Other Races	35	12		
Month 9	-6.57 (-12.25, -0.89)	0.05 (-9.69, 9.78)	-6.62 (-17.87, 4.64), 0.2474	-0.31 (-0.96, 0.34)
Month 18	-4.94 (-10.88, 1.00)	-0.40 (-10.63, 9.83)	-4.54 (-16.36, 7.27), 0.4490	-0.21 (-0.88, 0.46)
p-value of Treatment*Race	0.5294			

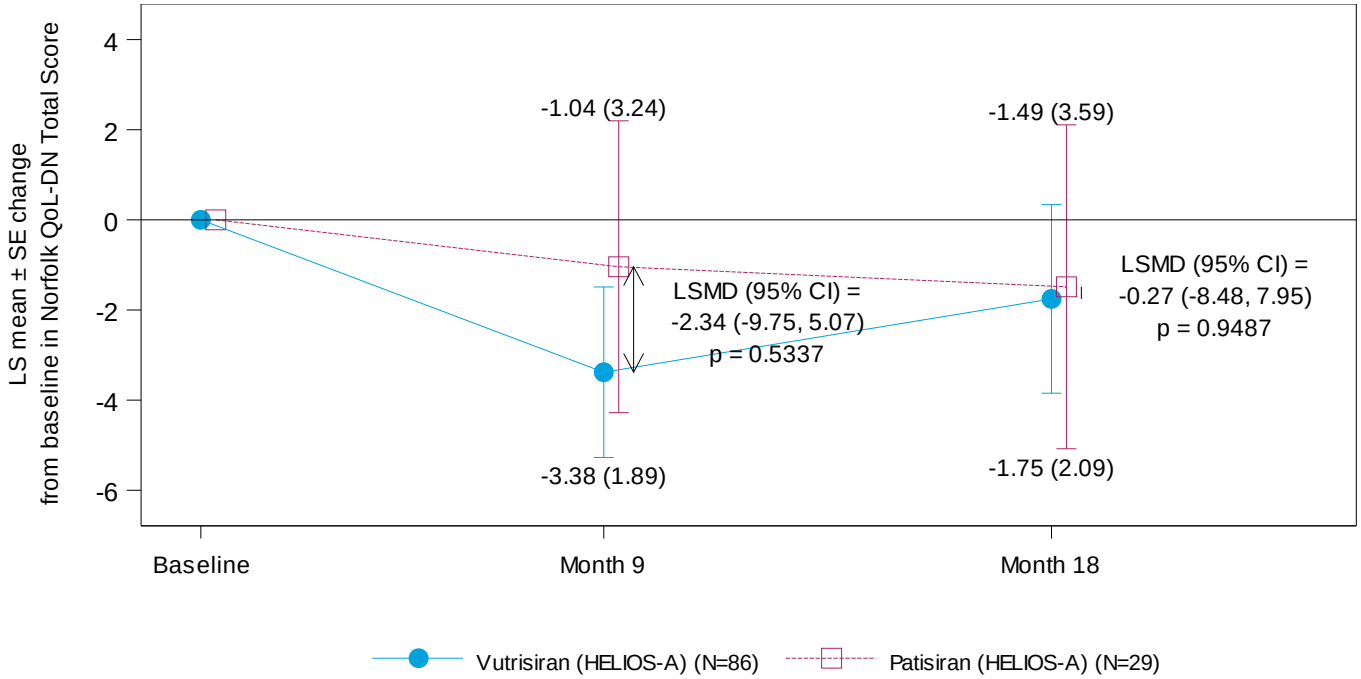
Norfolk QoL-DN score = composite of 35 quality of life questions; lower scores indicate higher quality of life (range = -4 to 136). Nonmissing scores for items 27-33 imputed for patients who reported an impact due to COVID-19 pandemic. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.
LS estimates and p-value derived from mixed-effects model for repeated measures (MMRM), controlling for categorical factors (treatment, visit), the subgroup variable, continuous covariate (baseline value), and interaction (treatment by visit, treatment by subgroup).
Standardized effect size (d) = LS mean difference/estimated pooled standard deviation with the small sample bias correction.

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

Alnylam Pharmaceuticals Inc.
ALN-TTRSC02-002

Norfolk Quality of Life - Diabetic Neuropathy (QoL-DN): Change from Baseline Over Time Series Plot
Subgroup Analysis: Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A)
mITT Population

Race: White



N evaluable			
Vutrisiran	85	81	80
Patisiran	29	28	27

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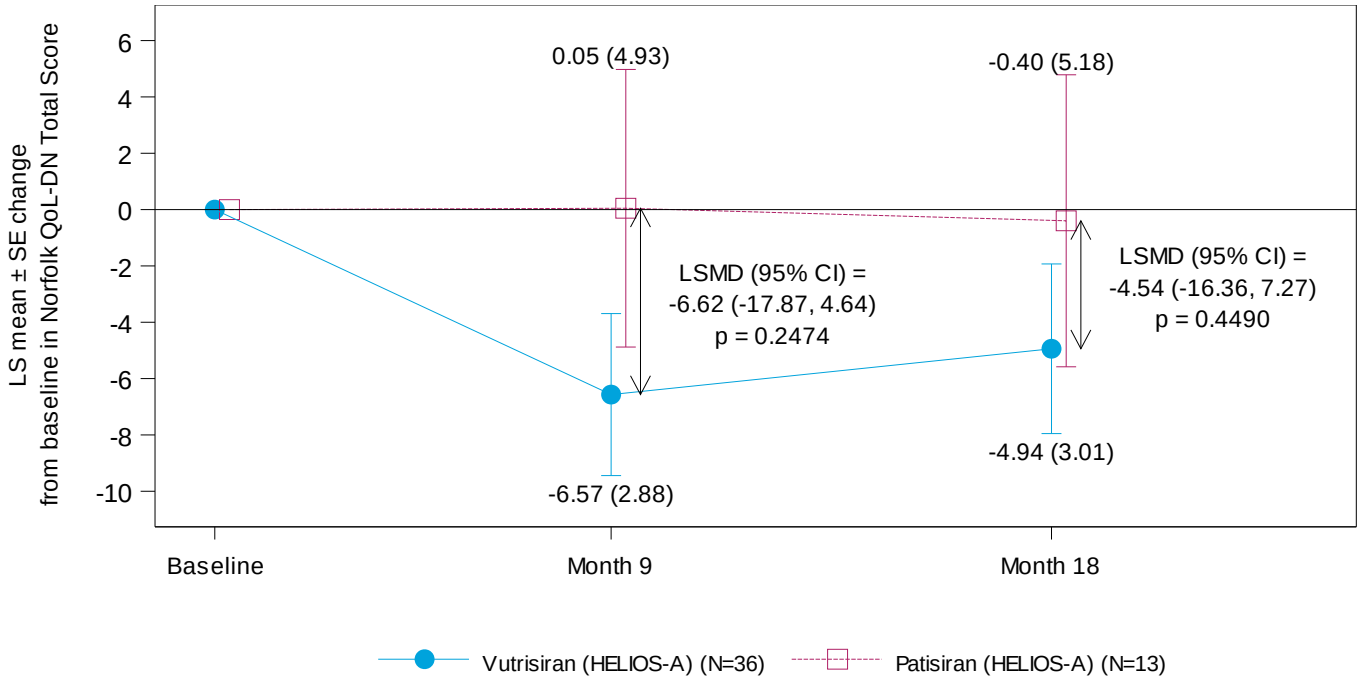
Alnylam Pharmaceuticals Inc.
ALN-TTRSC02-002

Norfolk Quality of Life - Diabetic Neuropathy (QoL-DN): Change from Baseline Over Time Series Plot
Subgroup Analysis: Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A)
mITT Population

Race: All Other Races



N evaluable			
Vutrisiran	36	34	33
Patisiran	13	12	11

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

Alnylam Pharmaceuticals Inc.
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Table 3.3
Norfolk Quality of Life - Diabetic Neuropathy (QoL-DN) Total Score: Change from Baseline to Month 18, MMRM Model
Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A) Subgroup Analysis
mITT Population

Subgroup Visit	LS Mean (95% CI) Vutrisiran (HELIOS-A) (N=122)	LS Mean (95% CI) Patisiran (HELIOS-A) (N=42)	LS Mean Difference (Vutrisiran-Patisiran) (95% CI), p-value	Standardized Effect Size (95% CI)
Region				
North America	26	8		
Month 9	-9.17 (-15.78, -2.56)	-4.03 (-15.73, 7.67)	-5.14 (-18.56, 8.28), 0.4504	-0.30 (-1.08, 0.49)
Month 18	-7.52 (-14.31, -0.73)	-4.46 (-16.55, 7.63)	-3.06 (-16.91, 10.79), 0.6633	-0.12 (-0.94, 0.70)
Western Europe	39	18		
Month 9	-3.54 (-8.85, 1.77)	-4.34 (-12.19, 3.50)	0.80 (-8.67, 10.28), 0.8672	0.05 (-0.50, 0.60)
Month 18	-1.89 (-7.45, 3.67)	-4.78 (-13.12, 3.57)	2.88 (-7.14, 12.91), 0.5709	0.19 (-0.37, 0.74)
Rest of World	52	14		
Month 9	-2.59 (-7.21, 2.02)	5.83 (-3.04, 14.71)	-8.43 (-18.44, 1.58), 0.0983	-0.45 (-1.04, 0.13)
Month 18	-0.95 (-5.87, 3.97)	5.40 (-3.95, 14.76)	-6.35 (-16.93, 4.23), 0.2379	-0.32 (-0.93, 0.29)
p-value of Treatment*Region	0.4025			

Norfolk QoL-DN score = composite of 35 quality of life questions; lower scores indicate higher quality of life (range = -4 to 136). Nonmissing scores for items 27-33 imputed for patients who reported an impact due to COVID-19 pandemic. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.
LS estimates and p-value derived from mixed-effects model for repeated measures (MMRM), controlling for categorical factors (treatment, visit), the subgroup variable, continuous covariate (baseline value), and interaction (treatment by visit, treatment by subgroup).
Standardized effect size (d) = LS mean difference/estimated pooled standard deviation with the small sample bias correction.

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

Alnylam Pharmaceuticals Inc.
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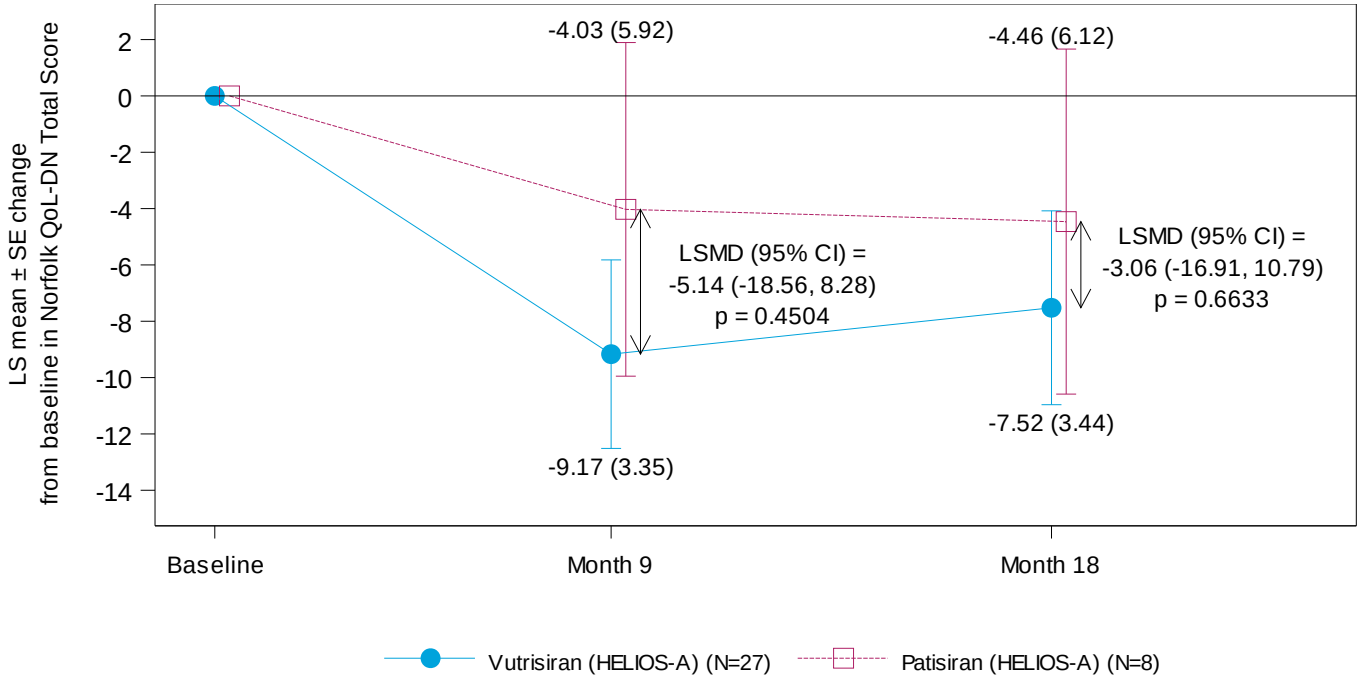
Norfolk Quality of Life - Diabetic Neuropathy (QoL-DN): Change from Baseline Over Time Series Plot
Subgroup Analysis: Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A)
mITT Population

Region: North America



N evaluable			
Vutrisiran	26	24	24
Patisiran	8	8	7

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

Alnylam Pharmaceuticals Inc.
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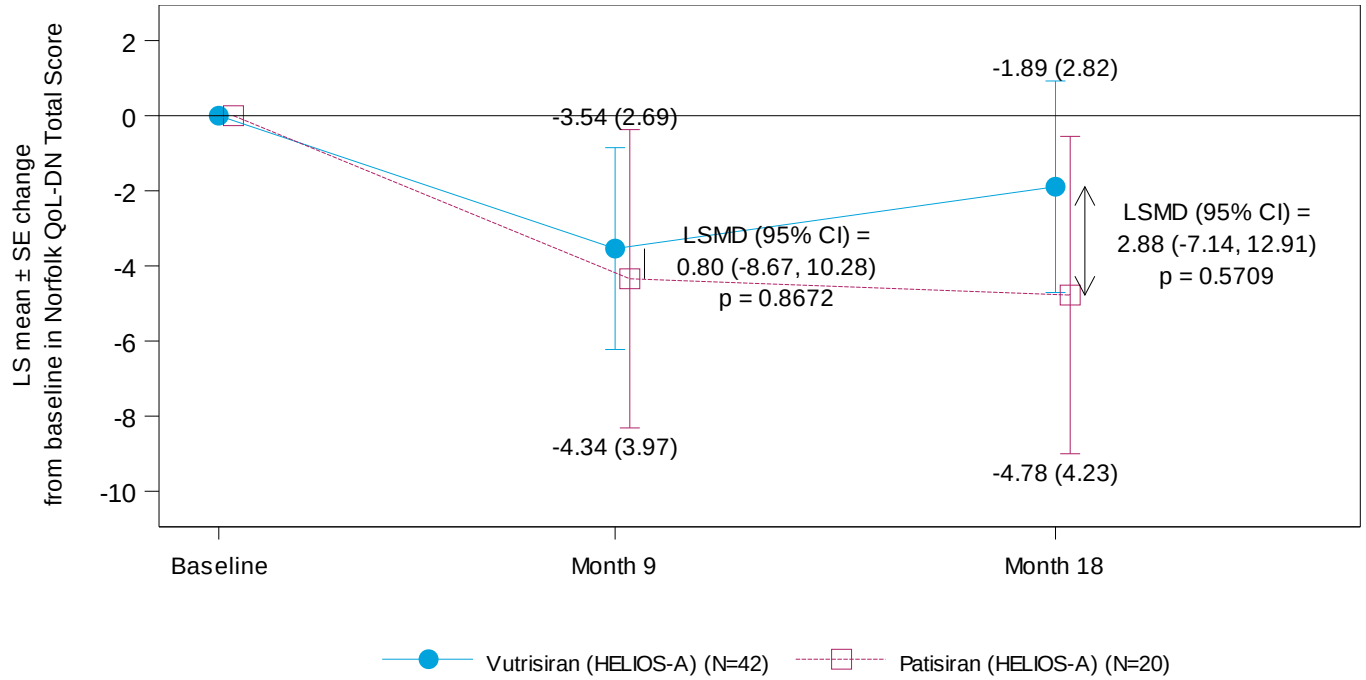
Norfolk Quality of Life - Diabetic Neuropathy (QoL-DN): Change from Baseline Over Time Series Plot
Subgroup Analysis: Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A)
mITT Population

Region: Western Europe



N evaluable			
Vutrisiran	42	39	39
Patisiran	20	18	18

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

Alnylam Pharmaceuticals Inc.
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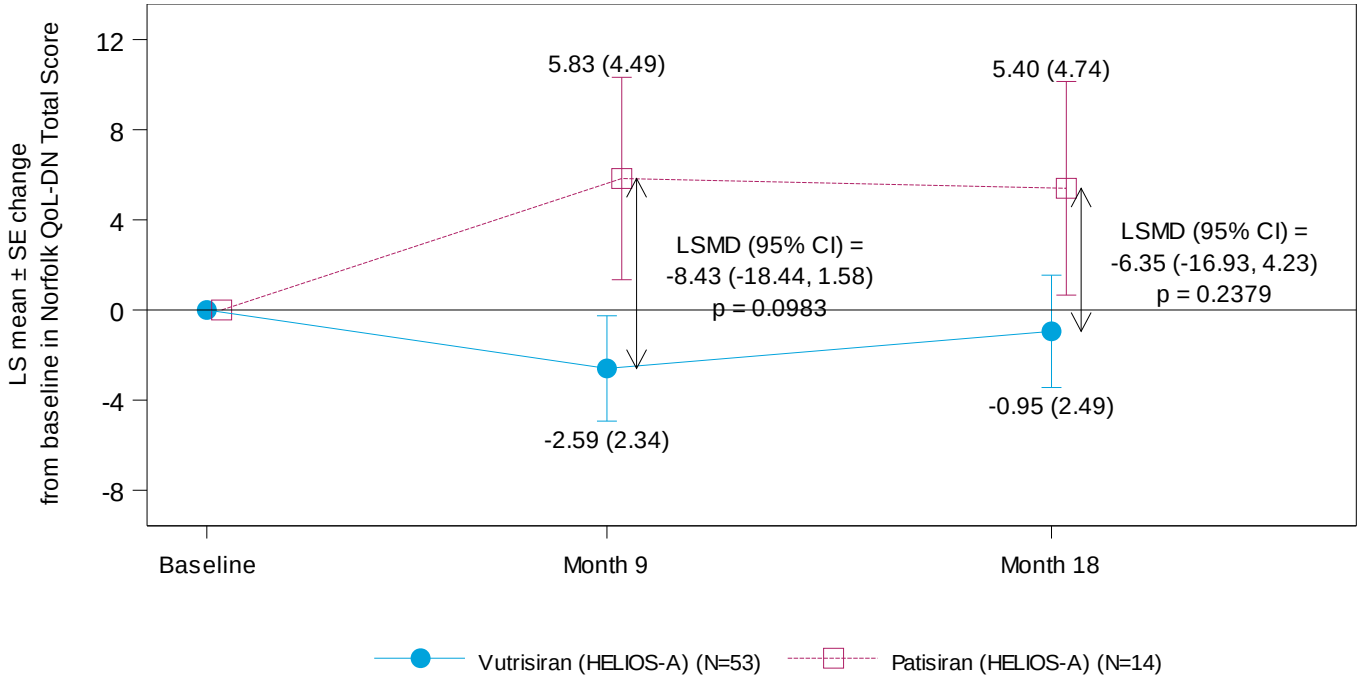
Norfolk Quality of Life - Diabetic Neuropathy (QoL-DN): Change from Baseline Over Time Series Plot
Subgroup Analysis: Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A)
mITT Population

Region: Rest of World



N evaluable			
Vutrisiran	53	52	50
Patisiran	14	14	13

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

Alnylam Pharmaceuticals Inc.
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Table 3.3
Norfolk Quality of Life - Diabetic Neuropathy (QoL-DN) Total Score: Change from Baseline to Month 18, MMRM Model
Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A) Subgroup Analysis
mITT Population

Subgroup Visit	LS Mean (95% CI) Vutrisiran (HELIOS-A) (N=122)	LS Mean (95% CI) Patisiran (HELIOS-A) (N=42)	LS Mean Difference (Vutrisiran-Patisiran) (95% CI), p-value	Standardized Effect Size (95% CI)
Baseline NIS				
<50	76	27		
Month 9	-11.51 (-15.09, -7.92)	-6.33 (-12.18, -0.47)	-5.18 (-11.89, 1.53), 0.1294	-0.35 (-0.78, 0.09)
Month 18	-9.94 (-13.87, -6.00)	-6.81 (-13.32, -0.31)	-3.12 (-10.58, 4.33), 0.4094	-0.17 (-0.62, 0.27)
≥50	41	13		
Month 9	8.69 (3.74, 13.63)	10.76 (2.31, 19.21)	-2.08 (-11.52, 7.36), 0.6647	-0.13 (-0.75, 0.49)
Month 18	10.26 (5.08, 15.43)	10.28 (1.36, 19.19)	-0.02 (-10.01, 9.97), 0.9967	-0.00 (-0.64, 0.64)
p-value of Treatment*Baseline NIS	0.5912			

Norfolk QoL-DN score = composite of 35 quality of life questions; lower scores indicate higher quality of life (range = -4 to 136). Nonmissing scores for items 27-33 imputed for patients who reported an impact due to COVID-19 pandemic. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.
LS estimates and p-value derived from mixed-effects model for repeated measures (MMRM), controlling for categorical factors (treatment, visit), the subgroup variable, continuous covariate (baseline value), and interaction (treatment by visit, treatment by subgroup).
Standardized effect size (d) = LS mean difference/estimated pooled standard deviation with the small sample bias correction.

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

Alnylam Pharmaceuticals Inc.
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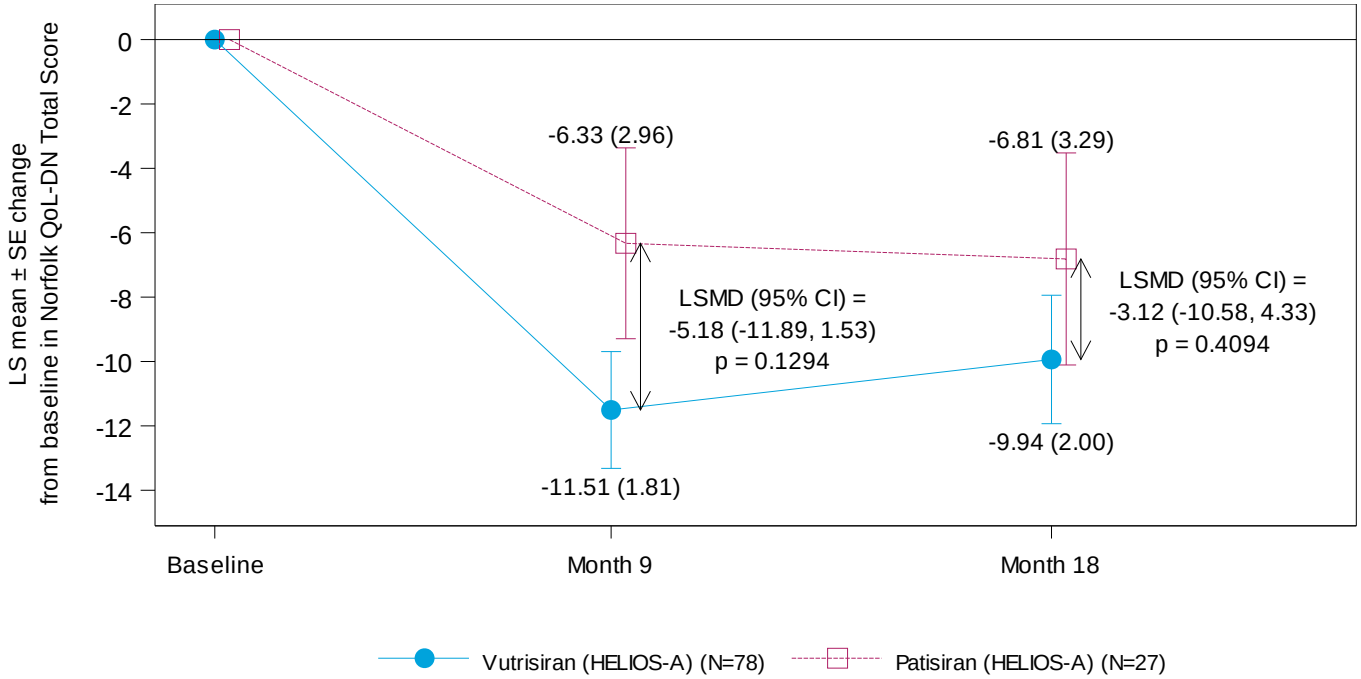
Norfolk Quality of Life - Diabetic Neuropathy (QoL-DN): Change from Baseline Over Time Series Plot
Subgroup Analysis: Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A)
mITT Population

Baseline NIS: <50



N evaluable

Vutrisiran	77	76	74
Patisiran	27	27	26

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

Alnylam Pharmaceuticals Inc.
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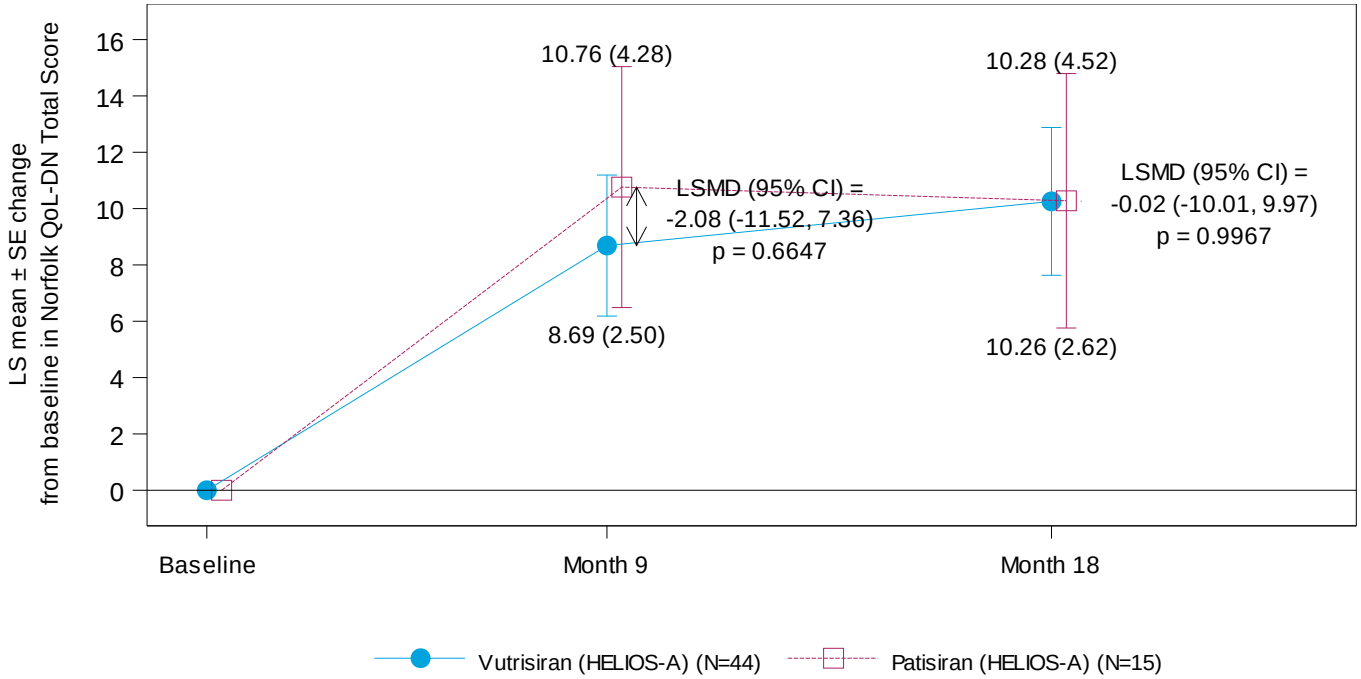
Norfolk Quality of Life - Diabetic Neuropathy (QoL-DN): Change from Baseline Over Time Series Plot
Subgroup Analysis: Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A)
mITT Population

Baseline NIS: ≥50



N evaluable			
Vutrisiran	44	39	39
Patisiran	15	13	12

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

Alnylam Pharmaceuticals Inc.
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Table 3.3
Norfolk Quality of Life - Diabetic Neuropathy (QoL-DN) Total Score: Change from Baseline to Month 18, MMRM Model
Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A) Subgroup Analysis
mITT Population

Subgroup Visit	LS Mean (95% CI) Vutrisiran (HELIOS-A) (N=122)	LS Mean (95% CI) Patisiran (HELIOS-A) (N=42)	LS Mean Difference (Vutrisiran-Patisiran) (95% CI), p-value	Standardized Effect Size (95% CI)
Previous Tetramer Stabilizer Use				
Yes	74	32		
Month 9	-2.26 (-6.16, 1.64)	-0.58 (-6.54, 5.37)	-1.68 (-8.80, 5.45), 0.6429	-0.10 (-0.51, 0.31)
Month 18	-0.60 (-4.87, 3.66)	-1.03 (-7.68, 5.62)	0.43 (-7.48, 8.34), 0.9152	0.02 (-0.40, 0.44)
No	43	8		
Month 9	-7.95 (-13.07, -2.84)	-1.24 (-13.03, 10.56)	-6.72 (-19.58, 6.15), 0.3038	-0.36 (-1.11, 0.39)
Month 18	-6.30 (-11.66, -0.94)	-1.68 (-13.88, 10.51)	-4.62 (-17.95, 8.72), 0.4953	-0.21 (-1.00, 0.58)
p-value of Treatment*Previous Tetramer Stabilizer Use	0.4967			

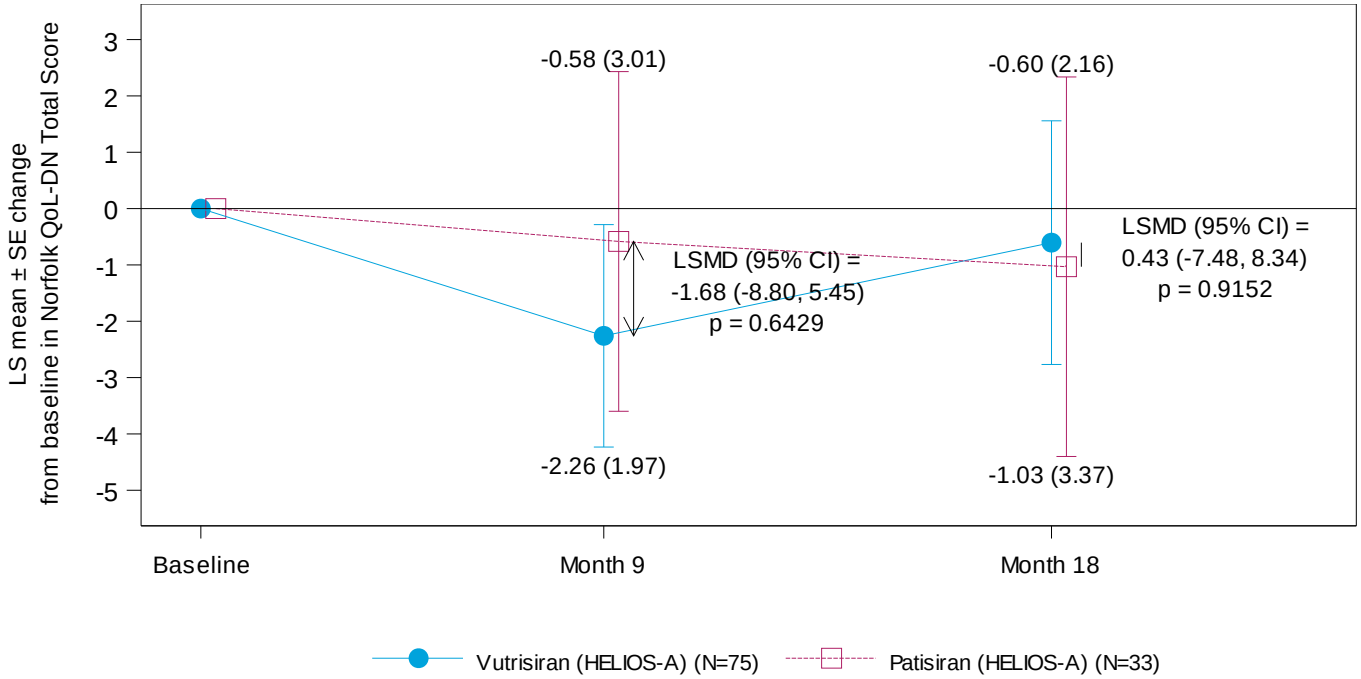
Norfolk QoL-DN score = composite of 35 quality of life questions; lower scores indicate higher quality of life (range = -4 to 136). Nonmissing scores for items 27-33 imputed for patients who reported an impact due to COVID-19 pandemic. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.
LS estimates and p-value derived from mixed-effects model for repeated measures (MMRM), controlling for categorical factors (treatment, visit), the subgroup variable, continuous covariate (baseline value), and interaction (treatment by visit, treatment by subgroup).
Standardized effect size (d) = LS mean difference/estimated pooled standard deviation with the small sample bias correction.

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

Alnylam Pharmaceuticals Inc.
ALN-TTRSC02-002

Norfolk Quality of Life - Diabetic Neuropathy (QoL-DN): Change from Baseline Over Time Series Plot
Subgroup Analysis: Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A)
mITT Population

Previous Tetramer Stabilizer Use: Yes



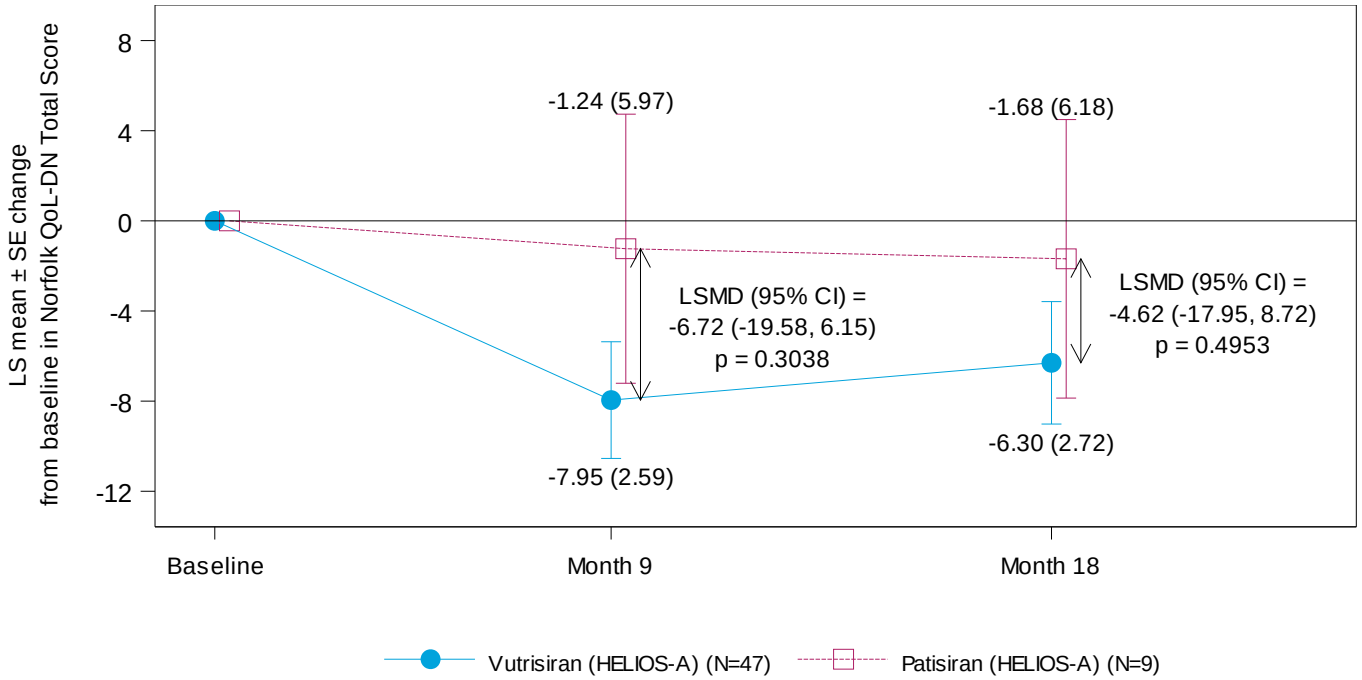
N evaluable			
Vutrisiran	75	74	71
Patisiran	33	32	31

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

Alnylam Pharmaceuticals Inc.
ALN-TTRSC02-002

Norfolk Quality of Life - Diabetic Neuropathy (QoL-DN): Change from Baseline Over Time Series Plot
Subgroup Analysis: Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A)
mITT Population

Previous Tetramer Stabilizer Use: No



N evaluable			
Vutrisiran	46	41	42
Patisiran	9	8	7

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

Alnylam Pharmaceuticals Inc.
ALN-TTRSC02-002

Table 3.3
Norfolk Quality of Life - Diabetic Neuropathy (QoL-DN) Total Score: Change from Baseline to Month 18, MMRM Model
Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A) Subgroup Analysis
mITT Population

Subgroup Visit	LS Mean (95% CI) Vutrisiran (HELIOS-A) (N=122)	LS Mean (95% CI) Patisiran (HELIOS-A) (N=42)	LS Mean Difference (Vutrisiran-Patisiran) (95% CI), p-value	Standardized Effect Size (95% CI)
Genotype				
V30M	52	20		
Month 9	-5.33 (-9.99, -0.66)	-3.16 (-10.70, 4.37)	-2.16 (-11.03, 6.70), 0.6305	-0.16 (-0.67, 0.35)
Month 18	-3.70 (-8.66, 1.27)	-3.58 (-11.67, 4.50)	-0.11 (-9.60, 9.37), 0.9813	-0.01 (-0.52, 0.50)
non-V30M	65	20		
Month 9	-3.53 (-7.71, 0.66)	1.74 (-5.80, 9.28)	-5.26 (-13.88, 3.35), 0.2294	-0.27 (-0.76, 0.23)
Month 18	-1.90 (-6.43, 2.63)	1.31 (-6.84, 9.47)	-3.21 (-12.53, 6.10), 0.4973	-0.15 (-0.67, 0.37)
p-value of Treatment*Genotype	0.6176			

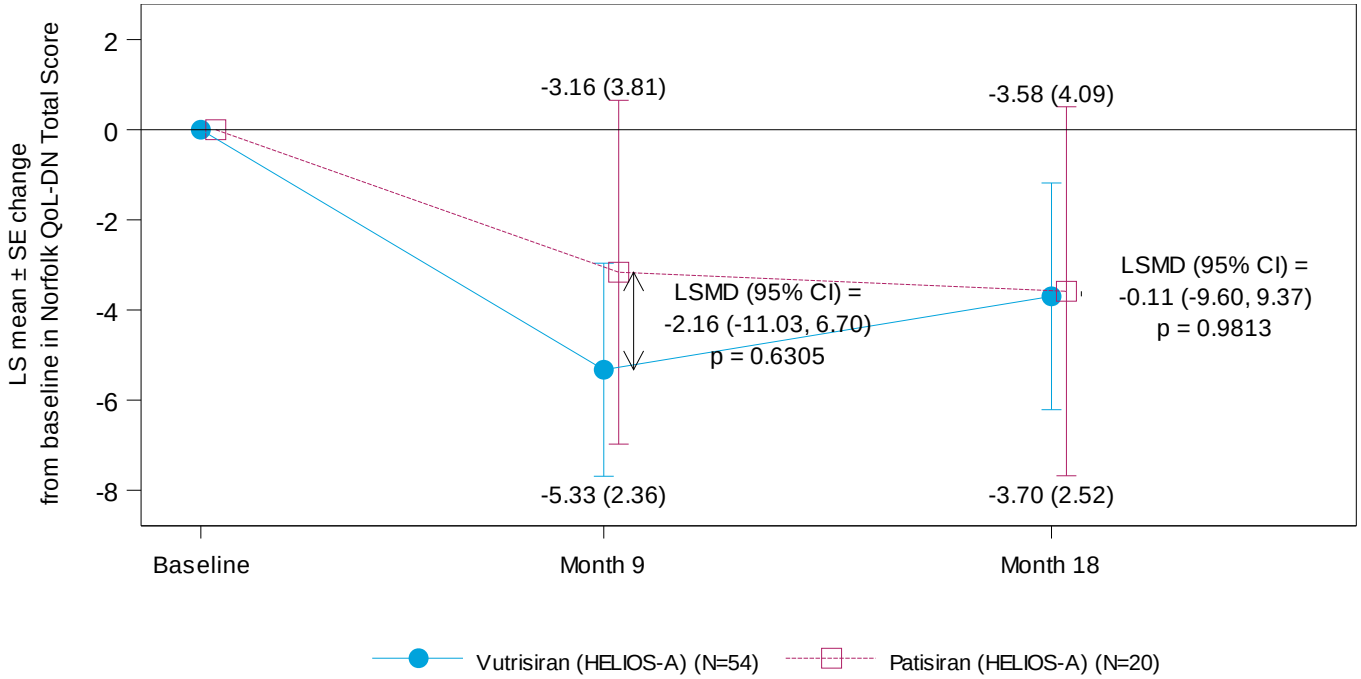
Norfolk QoL-DN score = composite of 35 quality of life questions; lower scores indicate higher quality of life (range = -4 to 136). Nonmissing scores for items 27-33 imputed for patients who reported an impact due to COVID-19 pandemic. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.
LS estimates and p-value derived from mixed-effects model for repeated measures (MMRM), controlling for categorical factors (treatment, visit), the subgroup variable, continuous covariate (baseline value), and interaction (treatment by visit, treatment by subgroup).
Standardized effect size (d) = LS mean difference/estimated pooled standard deviation with the small sample bias correction.

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

Alnylam Pharmaceuticals Inc.
ALN-TTRSC02-002

Norfolk Quality of Life - Diabetic Neuropathy (QoL-DN): Change from Baseline Over Time Series Plot
Subgroup Analysis: Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A)
mITT Population

Genotype: V30M



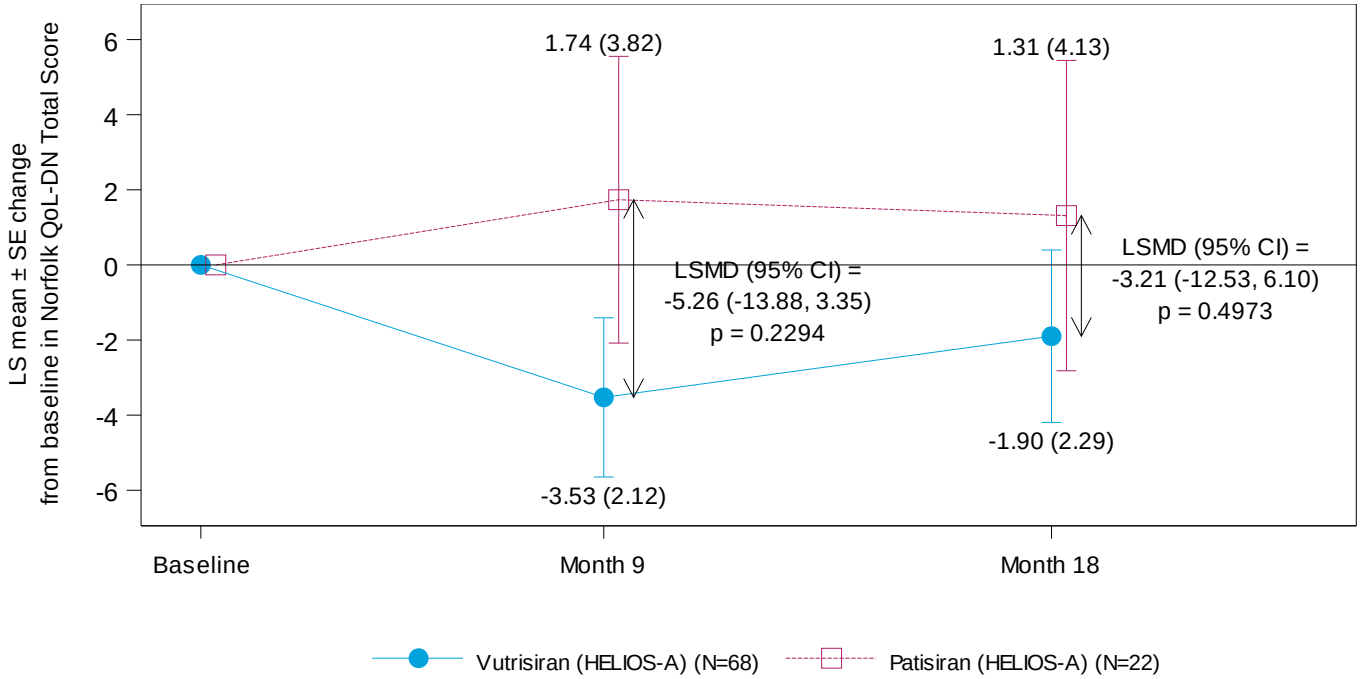
N evaluable			
Vutrisiran	53	51	51
Patisiran	20	20	20

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

Alnylam Pharmaceuticals Inc.
ALN-TTRSC02-002

Norfolk Quality of Life - Diabetic Neuropathy (QoL-DN): Change from Baseline Over Time Series Plot
Subgroup Analysis: Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A)
mITT Population

Genotype: non-V30M



N evaluable			
Vutrisiran	68	64	62
Patisiran	22	20	18

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

Alnylam Pharmaceuticals Inc.
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Table 3.3
Norfolk Quality of Life - Diabetic Neuropathy (QoL-DN) Total Score: Change from Baseline to Month 18, MMRM Model
Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A) Subgroup Analysis
mITT Population

Subgroup Visit	LS Mean (95% CI) Vutrisiran (HELIOS-A) (N=122)	LS Mean (95% CI) Patisiran (HELIOS-A) (N=42)	LS Mean Difference (Vutrisiran-Patisiran) (95% CI), p-value	Standardized Effect Size (95% CI)
FAP Stage				
I	82	30		
Month 9	-8.79 (-12.36, -5.21)	-5.07 (-10.90, 0.76)	-3.71 (-10.48, 3.05), 0.2795	-0.25 (-0.67, 0.17)
Month 18	-7.15 (-11.05, -3.26)	-5.40 (-11.81, 1.00)	-1.75 (-9.17, 5.68), 0.6429	-0.10 (-0.52, 0.32)
II&III	35	10		
Month 9	5.80 (0.33, 11.26)	12.22 (2.15, 22.28)	-6.42 (-17.63, 4.78), 0.2593	-0.34 (-1.03, 0.36)
Month 18	7.43 (1.76, 13.11)	11.89 (1.38, 22.39)	-4.46 (-16.16, 7.25), 0.4538	-0.21 (-0.97, 0.55)
p-value of Treatment*FAP Stage	0.6792			

Norfolk QoL-DN score = composite of 35 quality of life questions; lower scores indicate higher quality of life (range = -4 to 136). Nonmissing scores for items 27-33 imputed for patients who reported an impact due to COVID-19 pandemic. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.
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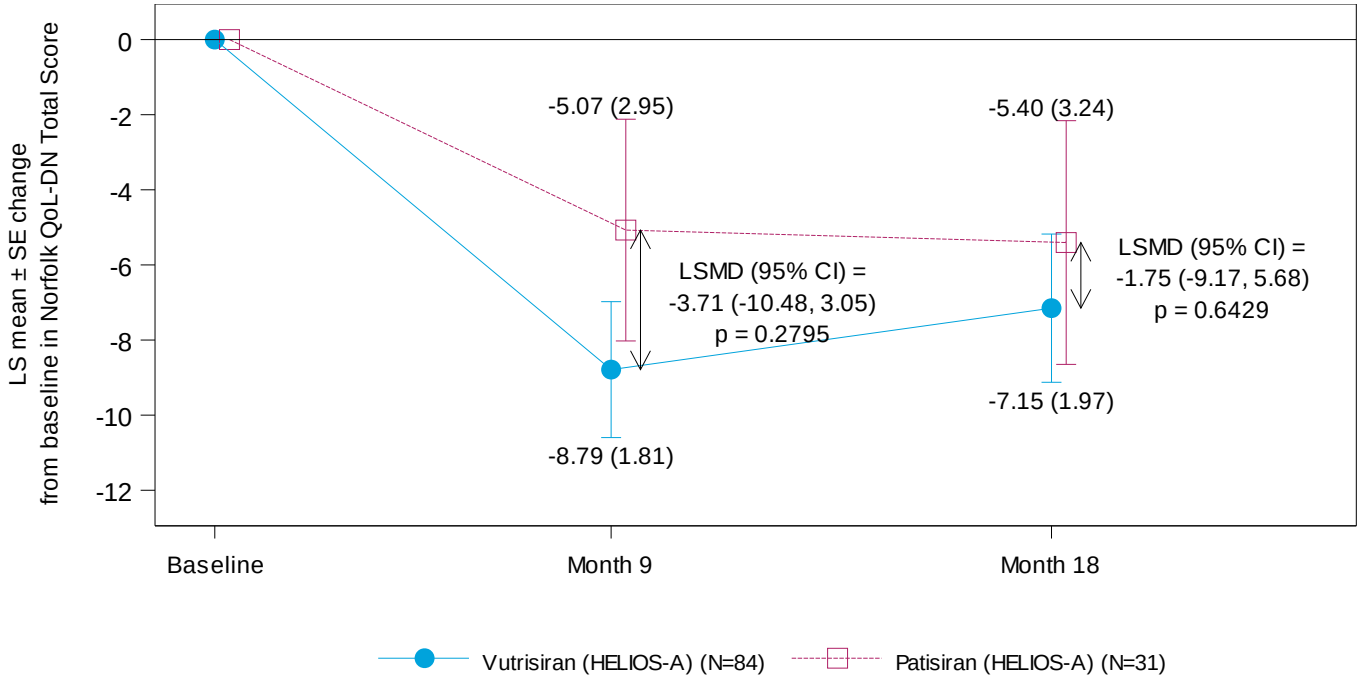
Standardized effect size (d) = LS mean difference/estimated pooled standard deviation with the small sample bias correction.

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

Alnylam Pharmaceuticals Inc.
ALN-TTRSC02-002

Norfolk Quality of Life - Diabetic Neuropathy (QoL-DN): Change from Baseline Over Time Series Plot
Subgroup Analysis: Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A)
mITT Population

FAP Stage: I



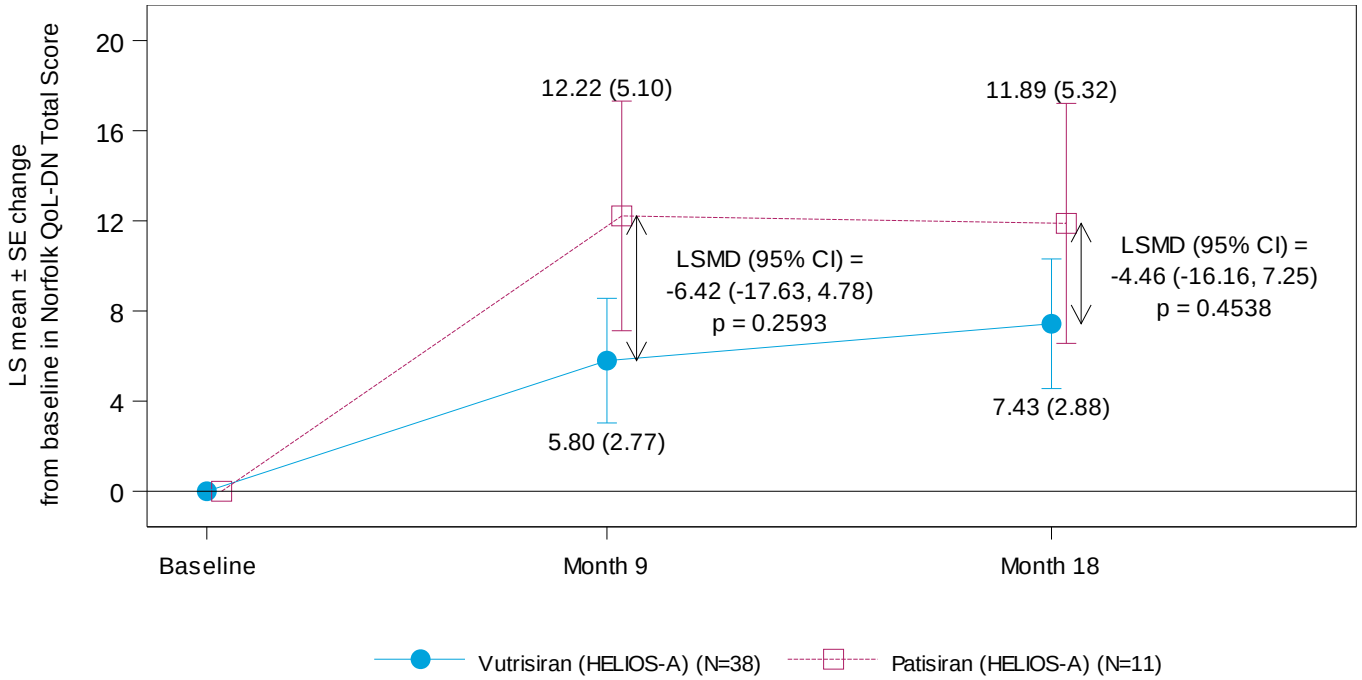
N evaluable			
Vutrisiran	83	81	80
Patisiran	31	30	30

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

Alnylam Pharmaceuticals Inc.
ALN-TTRSC02-002

Norfolk Quality of Life - Diabetic Neuropathy (QoL-DN): Change from Baseline Over Time Series Plot
Subgroup Analysis: Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A)
mITT Population

FAP Stage: II&III



N evaluable			
Vutrisiran	38	34	33
Patisiran	11	10	8

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

Alnylam Pharmaceuticals Inc.
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Table 3.3
Norfolk Quality of Life - Diabetic Neuropathy (QoL-DN) Total Score: Change from Baseline to Month 18, MMRM Model
Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A) Subgroup Analysis
mITT Population

Subgroup Visit	LS Mean (95% CI) Vutrisiran (HELIOS-A) (N=122)	LS Mean (95% CI) Patisiran (HELIOS-A) (N=42)	LS Mean Difference (Vutrisiran-Patisiran) (95% CI), p-value	Standardized Effect Size (95% CI)
Cardiac Subpopulation				
Yes	38	14		
Month 9	-3.21 (-8.60, 2.18)	7.47 (-1.44, 16.38)	-10.68 (-21.04, -0.32), 0.0434	-0.55 (-1.16, 0.07)
Month 18	-1.58 (-7.22, 4.05)	7.03 (-2.33, 16.40)	-8.62 (-19.50, 2.27), 0.1200	-0.39 (-1.01, 0.24)
No	79	26		
Month 9	-4.91 (-8.71, -1.11)	-5.13 (-11.71, 1.44)	0.22 (-7.34, 7.79), 0.9533	0.01 (-0.43, 0.46)
Month 18	-3.28 (-7.41, 0.85)	-5.57 (-12.74, 1.61)	2.29 (-5.96, 10.54), 0.5846	0.13 (-0.32, 0.58)
p-value of Treatment*Cardiac Subpopulation	0.0910			

Norfolk QoL-DN score = composite of 35 quality of life questions; lower scores indicate higher quality of life (range = -4 to 136). Nonmissing scores for items 27-33 imputed for patients who reported an impact due to COVID-19 pandemic. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.
LS estimates and p-value derived from mixed-effects model for repeated measures (MMRM), controlling for categorical factors (treatment, visit), the subgroup variable, continuous covariate (baseline value), and interaction (treatment by visit, treatment by subgroup).
Standardized effect size (d) = LS mean difference/estimated pooled standard deviation with the small sample bias correction.

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

Alnylam Pharmaceuticals Inc.
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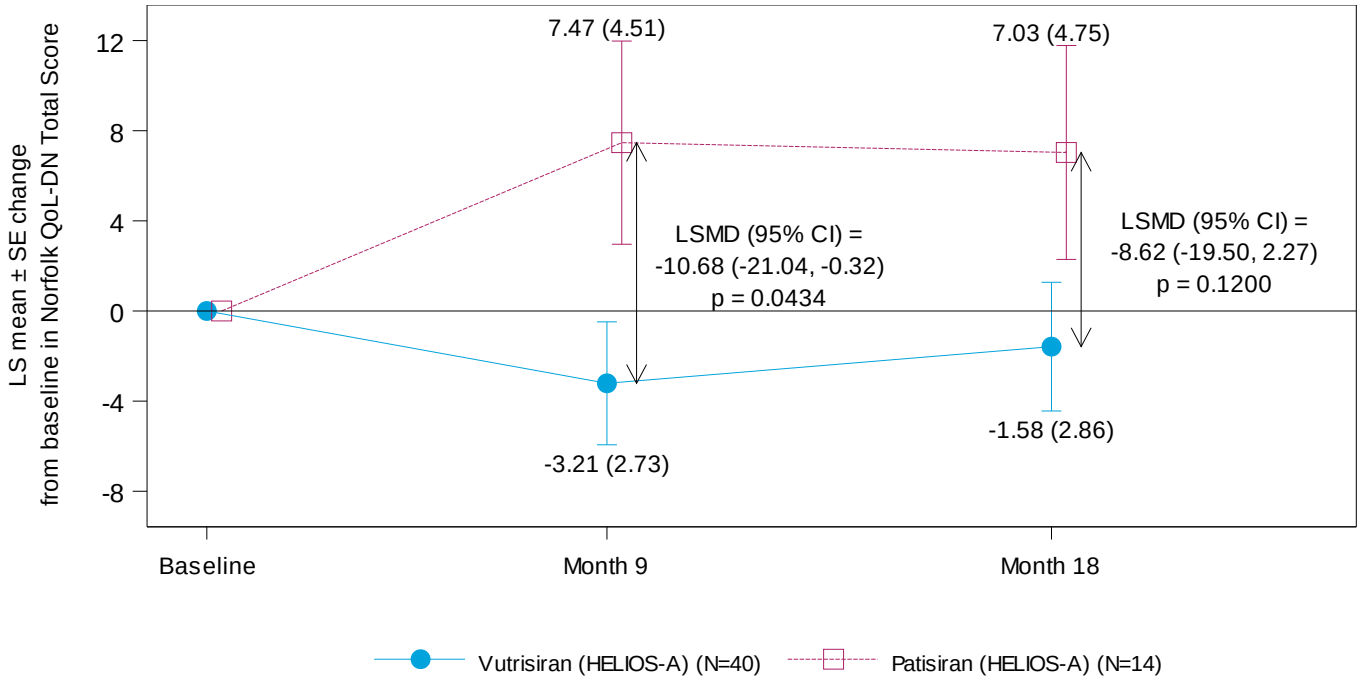
Norfolk Quality of Life - Diabetic Neuropathy (QoL-DN): Change from Baseline Over Time Series Plot
Subgroup Analysis: Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A)
mITT Population

Cardiac Subpopulation: Yes



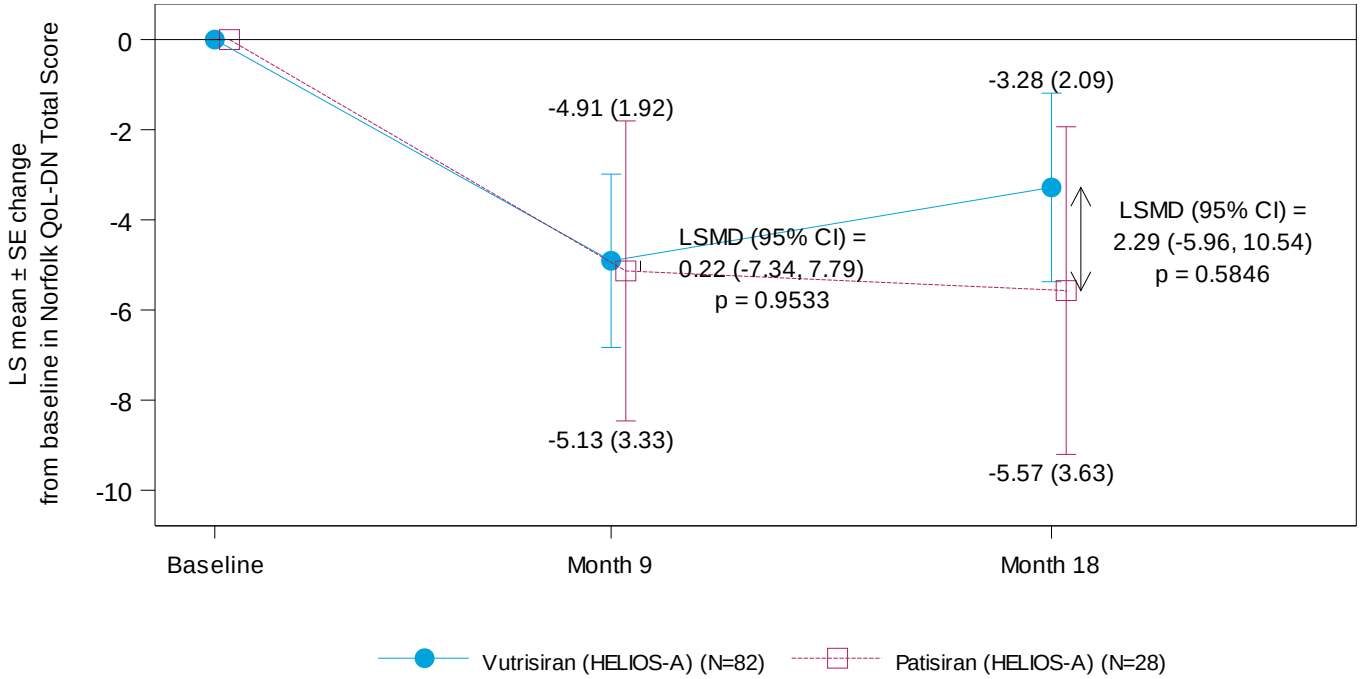
N evaluable			
Vutrisiran	40	38	37
Patisiran	14	14	13

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

Alnylam Pharmaceuticals Inc.
ALN-TTRSC02-002

Norfolk Quality of Life - Diabetic Neuropathy (QoL-DN): Change from Baseline Over Time Series Plot
Subgroup Analysis: Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A)
mITT Population

Cardiac Subpopulation: No



N evaluable			
Vutrisiran	81	77	76
Patisiran	28	26	25

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

Alnylam Pharmaceuticals Inc.
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Table 3.3
Norfolk Quality of Life - Diabetic Neuropathy (QoL-DN) Total Score: Change from Baseline to Month 18, MMRM Model
Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A) Subgroup Analysis
mITT Population

Subgroup Visit	LS Mean (95% CI) Vutrisiran (HELIOS-A) (N=122)	LS Mean (95% CI) Patisiran (HELIOS-A) (N=42)	LS Mean Difference (Vutrisiran-Patisiran) (95% CI), p-value	Standardized Effect Size (95% CI)
Weight (kg)				
<65	44	15		
Month 9	-2.66 (-7.72, 2.40)	-2.16 (-10.82, 6.49)	-0.50 (-10.52, 9.53), 0.9223	-0.03 (-0.61, 0.55)
Month 18	-1.02 (-6.38, 4.33)	-2.60 (-11.74, 6.53)	1.58 (-9.01, 12.16), 0.7688	0.09 (-0.50, 0.67)
≥65	73	25		
Month 9	-5.35 (-9.33, -1.37)	0.15 (-6.60, 6.90)	-5.51 (-13.34, 2.32), 0.1668	-0.33 (-0.78, 0.13)
Month 18	-3.72 (-8.04, 0.60)	-0.29 (-7.70, 7.12)	-3.43 (-12.00, 5.14), 0.4305	-0.17 (-0.64, 0.30)
p-value of Treatment*Weight	0.4322			

Norfolk QoL-DN score = composite of 35 quality of life questions; lower scores indicate higher quality of life (range = -4 to 136). Nonmissing scores for items 27-33 imputed for patients who reported an impact due to COVID-19 pandemic. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.
LS estimates and p-value derived from mixed-effects model for repeated measures (MMRM), controlling for categorical factors (treatment, visit), the subgroup variable, continuous covariate (baseline value), and interaction (treatment by visit, treatment by subgroup).
Standardized effect size (d) = LS mean difference/estimated pooled standard deviation with the small sample bias correction.

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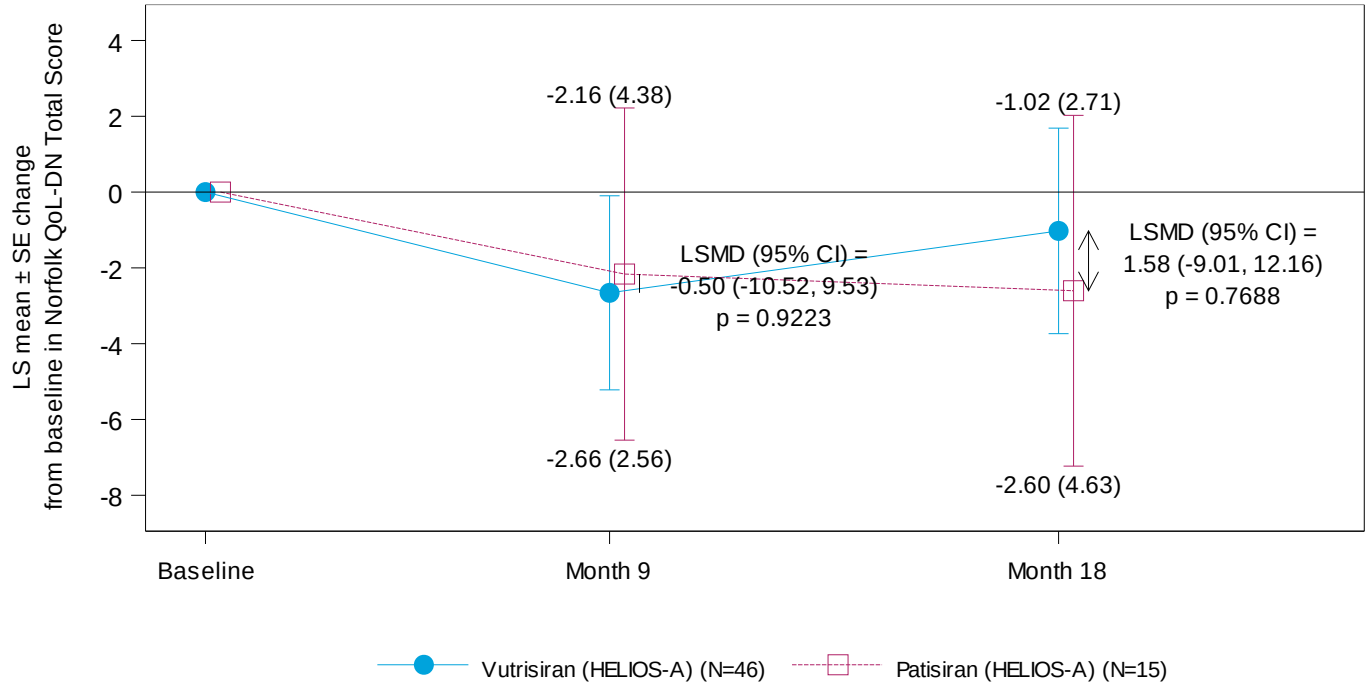
Norfolk Quality of Life - Diabetic Neuropathy (QoL-DN): Change from Baseline Over Time Series Plot
Subgroup Analysis: Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A)
mITT Population

Weight (kg): <65



N evaluable

Vutrisiran	46	44	42
Patisiran	15	15	15

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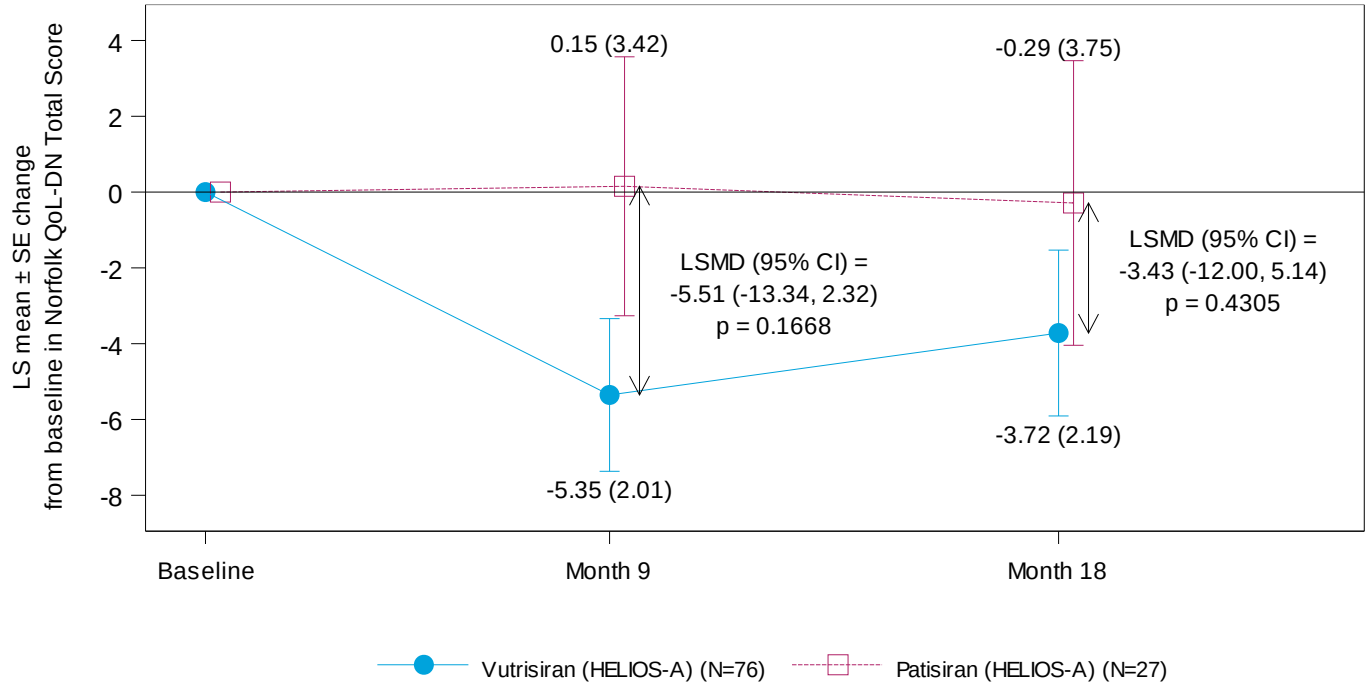
Norfolk Quality of Life - Diabetic Neuropathy (QoL-DN): Change from Baseline Over Time Series Plot
Subgroup Analysis: Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A)
mITT Population

Weight (kg): ≥65



N evaluable			
Vutrisiran	75	71	71
Patisiran	27	25	23

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Table 3.7
Norfolk Quality of Life - Diabetic Neuropathy (QoL-DN) Total Score: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Age (years): <65

Subgroup Visit	Vutrisiran (HELIOS-A) (N=76)	Patisiran (HELIOS-A) (N=31)
Baseline		
n	75	31
Mean (SD)	46.4 (26.8)	46.9 (28.8)
SE	3.1	5.2
Median	42.0	41.0
Min, Max	-1, 105	1, 125
Month 9		
Actual Value		
n	74	30
Mean (SD)	43.4 (27.7)	44.0 (27.5)
SE	3.2	5.0
Median	40.0	39.0
Min, Max	-4, 102	1, 115
Change from baseline		
n	73	30
Mean (SD)	-2.0 (19.0)	-1.6 (17.6)
SE	2.2	3.2
Median	-3.0	-5.0
Min, Max	-55, 52	-26, 54

Norfolk QoL-DN score = composite of 35 quality of life questions; lower scores indicate higher quality of life (range = -4 to 136). Nonmissing scores for items 27-33 imputed for patients who reported an impact due to COVID-19 pandemic. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

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Table 3.7
Norfolk Quality of Life - Diabetic Neuropathy (QoL-DN) Total Score: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Age (years): <65

Subgroup Visit	Vutrisiran (HELIOS-A) (N=76)	Patisiran (HELIOS-A) (N=31)
Month 18		
Actual Value		
n	74	29
Mean (SD)	42.6 (28.6)	42.7 (26.4)
SE	3.3	4.9
Median	40.0	40.0
Min, Max	0, 107	1, 99
Change from baseline		
n	73	29
Mean (SD)	-3.2 (21.9)	-0.2 (19.2)
SE	2.6	3.6
Median	-7.0	-2.0
Min, Max	-52, 58	-49, 58

Norfolk QoL-DN score = composite of 35 quality of life questions; lower scores indicate higher quality of life (range = -4 to 136). Nonmissing scores for items 27-33 imputed for patients who reported an impact due to COVID-19 pandemic. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

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Table 3.7
Norfolk Quality of Life - Diabetic Neuropathy (QoL-DN) Total Score: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Age (years): ≥65

Subgroup Visit	Vutrisiran (HELIOS-A) (N=46)	Patisiran (HELIOS-A) (N=11)
Baseline		
n	46	11
Mean (SD)	48.3 (25.7)	48.5 (34.5)
SE	3.8	10.4
Median	46.0	41.0
Min, Max	2, 102	3, 115
Month 9		
Actual Value		
n	42	10
Mean (SD)	38.2 (24.5)	52.7 (29.7)
SE	3.8	9.4
Median	40.0	60.0
Min, Max	0, 87	13, 90
Change from baseline		
n	42	10
Mean (SD)	-8.2 (16.9)	2.3 (19.8)
SE	2.6	6.2
Median	-2.0	1.0
Min, Max	-59, 28	-25, 43

Norfolk QoL-DN score = composite of 35 quality of life questions; lower scores indicate higher quality of life (range = -4 to 136). Nonmissing scores for items 27-33 imputed for patients who reported an impact due to COVID-19 pandemic. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 3.7
Norfolk Quality of Life - Diabetic Neuropathy (QoL-DN) Total Score: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Age (years): ≥65

Subgroup Visit	Vutrisiran (HELIOS-A) (N=46)	Patisiran (HELIOS-A) (N=11)
Month 18		
Actual Value		
n	40	9
Mean (SD)	44.5 (24.6)	49.7 (31.0)
SE	3.9	10.3
Median	43.5	55.0
Min, Max	2, 96	8, 85
Change from baseline		
n	40	9
Mean (SD)	-1.0 (20.5)	-2.0 (20.9)
SE	3.2	7.0
Median	-1.5	-2.0
Min, Max	-51, 67	-30, 40

Norfolk QoL-DN score = composite of 35 quality of life questions; lower scores indicate higher quality of life (range = -4 to 136). Nonmissing scores for items 27-33 imputed for patients who reported an impact due to COVID-19 pandemic. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 3.7
Norfolk Quality of Life - Diabetic Neuropathy (QoL-DN) Total Score: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Sex: Male

Subgroup Visit	Vutrisiran (HELIOS-A) (N=79)	Patisiran (HELIOS-A) (N=27)
Baseline		
n	78	27
Mean (SD)	47.0 (26.5)	46.9 (28.5)
SE	3.0	5.5
Median	42.0	41.0
Min, Max	3, 104	1, 125
Month 9		
Actual Value		
n	76	25
Mean (SD)	41.7 (27.3)	46.4 (29.5)
SE	3.1	5.9
Median	36.5	47.0
Min, Max	-4, 102	4, 115
Change from baseline		
n	75	25
Mean (SD)	-4.4 (20.0)	0.3 (19.5)
SE	2.3	3.9
Median	-3.0	-4.0
Min, Max	-59, 52	-26, 54

Norfolk QoL-DN score = composite of 35 quality of life questions; lower scores indicate higher quality of life (range = -4 to 136). Nonmissing scores for items 27-33 imputed for patients who reported an impact due to COVID-19 pandemic. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 3.7
Norfolk Quality of Life - Diabetic Neuropathy (QoL-DN) Total Score: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Sex: Male

Subgroup Visit	Vutrisiran (HELIOS-A) (N=79)	Patisiran (HELIOS-A) (N=27)
Month 18		
Actual Value		
n	74	23
Mean (SD)	44.7 (28.1)	44.0 (29.3)
SE	3.3	6.1
Median	41.5	45.0
Min, Max	0, 107	8, 99
Change from baseline		
n	73	23
Mean (SD)	-1.2 (23.5)	1.1 (19.0)
SE	2.7	4.0
Median	-2.0	-2.0
Min, Max	-52, 67	-26, 58

Norfolk QoL-DN score = composite of 35 quality of life questions; lower scores indicate higher quality of life (range = -4 to 136). Nonmissing scores for items 27-33 imputed for patients who reported an impact due to COVID-19 pandemic. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 3.7
Norfolk Quality of Life - Diabetic Neuropathy (QoL-DN) Total Score: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Sex: Female

Subgroup Visit	Vutrisiran (HELIOS-A) (N=43)	Patisiran (HELIOS-A) (N=15)
Baseline		
n	43	15
Mean (SD)	47.3 (26.3)	48.1 (33.3)
SE	4.0	8.6
Median	45.0	51.0
Min, Max	-1, 105	5, 115
Month 9		
Actual Value		
n	40	15
Mean (SD)	41.2 (25.4)	45.9 (26.1)
SE	4.0	6.7
Median	43.0	36.0
Min, Max	-1, 83	1, 90
Change from baseline		
n	40	15
Mean (SD)	-4.0 (15.4)	-2.2 (15.7)
SE	2.4	4.0
Median	-2.0	-5.0
Min, Max	-32, 39	-26, 21

Norfolk QoL-DN score = composite of 35 quality of life questions; lower scores indicate higher quality of life (range = -4 to 136). Nonmissing scores for items 27-33 imputed for patients who reported an impact due to COVID-19 pandemic. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 3.7
Norfolk Quality of Life - Diabetic Neuropathy (QoL-DN) Total Score: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Sex: Female

Subgroup Visit	Vutrisiran (HELIOS-A) (N=43)	Patisiran (HELIOS-A) (N=15)
Month 18		
Actual Value		
n	40	15
Mean (SD)	40.6 (25.5)	44.9 (24.8)
SE	4.0	6.4
Median	42.0	40.0
Min, Max	2, 89	1, 85
Change from baseline		
n	40	15
Mean (SD)	-4.7 (16.8)	-3.2 (20.2)
SE	2.7	5.2
Median	-5.0	-4.0
Min, Max	-42, 39	-49, 38

Norfolk QoL-DN score = composite of 35 quality of life questions; lower scores indicate higher quality of life (range = -4 to 136). Nonmissing scores for items 27-33 imputed for patients who reported an impact due to COVID-19 pandemic. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 3.7
Norfolk Quality of Life - Diabetic Neuropathy (QoL-DN) Total Score: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Race: White

Subgroup Visit	Vutrisiran (HELIOS-A) (N=86)	Patisiran (HELIOS-A) (N=29)
Baseline		
n	85	29
Mean (SD)	47.2 (27.6)	51.2 (31.0)
SE	3.0	5.8
Median	42.0	51.0
Min, Max	-1, 104	3, 125
Month 9		
Actual Value		
n	82	28
Mean (SD)	43.0 (26.9)	49.9 (28.6)
SE	3.0	5.4
Median	41.5	45.5
Min, Max	0, 102	7, 115
Change from baseline		
n	81	28
Mean (SD)	-2.7 (15.4)	-2.1 (17.8)
SE	1.7	3.4
Median	-1.0	-5.0
Min, Max	-34, 41	-26, 54

Norfolk QoL-DN score = composite of 35 quality of life questions; lower scores indicate higher quality of life (range = -4 to 136). Nonmissing scores for items 27-33 imputed for patients who reported an impact due to COVID-19 pandemic. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 3.7
Norfolk Quality of Life - Diabetic Neuropathy (QoL-DN) Total Score: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Race: White

Subgroup Visit	Vutrisiran (HELIOS-A) (N=86)	Patisiran (HELIOS-A) (N=29)
Month 18		
Actual Value		
n	81	27
Mean (SD)	43.0 (27.9)	46.5 (27.5)
SE	3.1	5.3
Median	42.0	45.0
Min, Max	2, 107	8, 99
Change from baseline		
n	80	27
Mean (SD)	-3.2 (19.9)	-2.8 (20.6)
SE	2.2	4.0
Median	-4.5	-2.0
Min, Max	-52, 44	-49, 58

Norfolk QoL-DN score = composite of 35 quality of life questions; lower scores indicate higher quality of life (range = -4 to 136). Nonmissing scores for items 27-33 imputed for patients who reported an impact due to COVID-19 pandemic. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 3.7
Norfolk Quality of Life - Diabetic Neuropathy (QoL-DN) Total Score: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Race: All Other Races

Subgroup Visit	Vutrisiran (HELIOS-A) (N=36)	Patisiran (HELIOS-A) (N=13)
Baseline		
n	36	13
Mean (SD)	46.9 (23.3)	38.7 (26.4)
SE	3.9	7.3
Median	45.0	40.0
Min, Max	3, 105	1, 86
Month 9		
Actual Value		
n	34	12
Mean (SD)	37.8 (25.8)	37.6 (25.1)
SE	4.4	7.3
Median	34.0	34.0
Min, Max	-4, 89	1, 84
Change from baseline		
n	34	12
Mean (SD)	-8.0 (24.0)	2.8 (18.8)
SE	4.1	5.4
Median	-7.5	-1.0
Min, Max	-59, 52	-21, 43

Norfolk QoL-DN score = composite of 35 quality of life questions; lower scores indicate higher quality of life (range = -4 to 136). Nonmissing scores for items 27-33 imputed for patients who reported an impact due to COVID-19 pandemic. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

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Table 3.7
Norfolk Quality of Life - Diabetic Neuropathy (QoL-DN) Total Score: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Race: All Other Races

Subgroup Visit	Vutrisiran (HELIOS-A) (N=36)	Patisiran (HELIOS-A) (N=13)
Month 18		
Actual Value		
n	33	11
Mean (SD)	43.9 (25.7)	39.1 (27.2)
SE	4.5	8.2
Median	42.0	34.0
Min, Max	0, 92	1, 81
Change from baseline		
n	33	11
Mean (SD)	-0.5 (24.8)	4.7 (15.3)
SE	4.3	4.6
Median	-3.0	3.0
Min, Max	-51, 67	-11, 40

Norfolk QoL-DN score = composite of 35 quality of life questions; lower scores indicate higher quality of life (range = -4 to 136). Nonmissing scores for items 27-33 imputed for patients who reported an impact due to COVID-19 pandemic. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

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Table 3.7
Norfolk Quality of Life - Diabetic Neuropathy (QoL-DN) Total Score: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Region: North America

Subgroup Visit	Vutrisiran (HELIOS-A) (N=27)	Patisiran (HELIOS-A) (N=8)
Baseline		
n	26	8
Mean (SD)	39.4 (26.5)	44.0 (26.4)
SE	5.2	9.3
Median	31.5	36.0
Min, Max	-1, 95	16, 88
Month 9		
Actual Value		
n	25	8
Mean (SD)	29.4 (22.6)	42.3 (31.7)
SE	4.5	11.2
Median	22.0	33.0
Min, Max	3, 83	7, 84
Change from baseline		
n	24	8
Mean (SD)	-8.0 (18.2)	-1.8 (22.0)
SE	3.7	7.8
Median	-4.5	-7.0
Min, Max	-55, 29	-26, 43

Norfolk QoL-DN score = composite of 35 quality of life questions; lower scores indicate higher quality of life (range = -4 to 136). Nonmissing scores for items 27-33 imputed for patients who reported an impact due to COVID-19 pandemic. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 3.7
Norfolk Quality of Life - Diabetic Neuropathy (QoL-DN) Total Score: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Region: North America

Subgroup Visit	Vutrisiran (HELIOS-A) (N=27)	Patisiran (HELIOS-A) (N=8)
Month 18		
Actual Value		
n	25	7
Mean (SD)	31.9 (26.0)	37.7 (31.4)
SE	5.2	11.9
Median	23.0	25.0
Min, Max	2, 84	9, 83
Change from baseline		
n	24	7
Mean (SD)	-5.8 (26.8)	-7.0 (28.3)
SE	5.5	10.7
Median	-9.5	-5.0
Min, Max	-52, 67	-49, 40

Norfolk QoL-DN score = composite of 35 quality of life questions; lower scores indicate higher quality of life (range = -4 to 136). Nonmissing scores for items 27-33 imputed for patients who reported an impact due to COVID-19 pandemic. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 3.7
Norfolk Quality of Life - Diabetic Neuropathy (QoL-DN) Total Score: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Region: Western Europe

Subgroup Visit	Vutrisiran (HELIOS-A) (N=42)	Patisiran (HELIOS-A) (N=20)
Baseline		
n	42	20
Mean (SD)	48.0 (27.3)	50.9 (28.1)
SE	4.2	6.3
Median	41.0	54.0
Min, Max	2, 104	3, 115
Month 9		
Actual Value		
n	39	18
Mean (SD)	43.1 (25.5)	44.7 (21.0)
SE	4.1	4.9
Median	42.0	42.0
Min, Max	0, 102	13, 90
Change from baseline		
n	39	18
Mean (SD)	-3.0 (18.0)	-5.4 (14.7)
SE	2.9	3.5
Median	-4.0	-6.5
Min, Max	-31, 41	-26, 17

Norfolk QoL-DN score = composite of 35 quality of life questions; lower scores indicate higher quality of life (range = -4 to 136). Nonmissing scores for items 27-33 imputed for patients who reported an impact due to COVID-19 pandemic. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

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Table 3.7
Norfolk Quality of Life - Diabetic Neuropathy (QoL-DN) Total Score: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Region: Western Europe

Subgroup Visit	Vutrisiran (HELIOS-A) (N=42)	Patisiran (HELIOS-A) (N=20)
Month 18		
Actual Value		
n	39	18
Mean (SD)	43.9 (24.8)	45.4 (23.4)
SE	4.0	5.5
Median	42.0	47.5
Min, Max	2, 94	8, 85
Change from baseline		
n	39	18
Mean (SD)	-2.3 (19.7)	-4.8 (11.6)
SE	3.2	2.7
Median	-5.0	-2.0
Min, Max	-42, 44	-30, 12

Norfolk QoL-DN score = composite of 35 quality of life questions; lower scores indicate higher quality of life (range = -4 to 136). Nonmissing scores for items 27-33 imputed for patients who reported an impact due to COVID-19 pandemic. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 3.7
Norfolk Quality of Life - Diabetic Neuropathy (QoL-DN) Total Score: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Region: Rest of World

Subgroup Visit	Vutrisiran (HELIOS-A) (N=53)	Patisiran (HELIOS-A) (N=14)
Baseline		
n	53	14
Mean (SD)	50.2 (25.2)	44.1 (35.5)
SE	3.5	9.5
Median	48.0	40.5
Min, Max	3, 105	1, 125
Month 9		
Actual Value		
n	52	14
Mean (SD)	46.1 (27.8)	50.4 (34.5)
SE	3.9	9.2
Median	45.0	47.0
Min, Max	-4, 97	1, 115
Change from baseline		
n	52	14
Mean (SD)	-3.5 (19.0)	6.2 (18.6)
SE	2.6	5.0
Median	-1.5	2.5
Min, Max	-59, 52	-18, 54

Norfolk QoL-DN score = composite of 35 quality of life questions; lower scores indicate higher quality of life (range = -4 to 136). Nonmissing scores for items 27-33 imputed for patients who reported an impact due to COVID-19 pandemic. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

Alnylam Pharmaceuticals Inc.
ALN-TTRSC02-002

Table 3.7
Norfolk Quality of Life - Diabetic Neuropathy (QoL-DN) Total Score: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Region: Rest of World

Subgroup Visit	Vutrisiran (HELIOS-A) (N=53)	Patisiran (HELIOS-A) (N=14)
Month 18		
Actual Value		
n	50	13
Mean (SD)	48.4 (28.4)	46.5 (31.5)
SE	4.0	8.7
Median	51.0	43.0
Min, Max	0, 107	1, 99
Change from baseline		
n	50	13
Mean (SD)	-0.9 (19.9)	8.6 (20.5)
SE	2.8	5.7
Median	-1.5	4.0
Min, Max	-51, 58	-11, 58

Norfolk QoL-DN score = composite of 35 quality of life questions; lower scores indicate higher quality of life (range = -4 to 136). Nonmissing scores for items 27-33 imputed for patients who reported an impact due to COVID-19 pandemic. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

Alnylam Pharmaceuticals Inc.
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Table 3.7
Norfolk Quality of Life - Diabetic Neuropathy (QoL-DN) Total Score: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Baseline NIS: <50

Subgroup Visit	Vutrisiran (HELIOS-A) (N=78)	Patisiran (HELIOS-A) (N=27)
Baseline		
n	77	27
Mean (SD)	37.4 (23.2)	36.7 (24.4)
SE	2.6	4.7
Median	34.0	34.0
Min, Max	-1, 95	1, 88
Month 9		
Actual Value		
n	77	27
Mean (SD)	29.3 (20.5)	34.9 (22.2)
SE	2.3	4.3
Median	26.0	33.0
Min, Max	-4, 83	1, 84
Change from baseline		
n	76	27
Mean (SD)	-7.2 (17.4)	-1.7 (16.6)
SE	2.0	3.2
Median	-6.0	-5.0
Min, Max	-59, 41	-26, 43

Norfolk QoL-DN score = composite of 35 quality of life questions; lower scores indicate higher quality of life (range = -4 to 136). Nonmissing scores for items 27-33 imputed for patients who reported an impact due to COVID-19 pandemic. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

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Table 3.7
Norfolk Quality of Life - Diabetic Neuropathy (QoL-DN) Total Score: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Baseline NIS: <50

Subgroup Visit	Vutrisiran (HELIOS-A) (N=78)	Patisiran (HELIOS-A) (N=27)
Month 18		
Actual Value		
n	75	26
Mean (SD)	30.9 (22.4)	34.0 (24.1)
SE	2.6	4.7
Median	25.0	27.0
Min, Max	0, 89	1, 83
Change from baseline		
n	74	26
Mean (SD)	-5.3 (21.0)	-2.5 (18.5)
SE	2.4	3.6
Median	-7.5	-3.0
Min, Max	-52, 67	-49, 40

Norfolk QoL-DN score = composite of 35 quality of life questions; lower scores indicate higher quality of life (range = -4 to 136). Nonmissing scores for items 27-33 imputed for patients who reported an impact due to COVID-19 pandemic. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

Alnylam Pharmaceuticals Inc.
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Table 3.7
Norfolk Quality of Life - Diabetic Neuropathy (QoL-DN) Total Score: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Baseline NIS: ≥50

Subgroup Visit	Vutrisiran (HELIOS-A) (N=44)	Patisiran (HELIOS-A) (N=15)
Baseline		
n	44	15
Mean (SD)	64.1 (22.6)	66.5 (30.0)
SE	3.4	7.7
Median	65.0	65.0
Min, Max	21, 105	10, 125
Month 9		
Actual Value		
n	39	13
Mean (SD)	65.6 (20.0)	69.6 (24.2)
SE	3.2	6.7
Median	70.0	73.0
Min, Max	24, 102	31, 115
Change from baseline		
n	39	13
Mean (SD)	1.5 (19.3)	1.7 (21.1)
SE	3.1	5.9
Median	1.0	0.0
Min, Max	-35, 52	-25, 54

Norfolk QoL-DN score = composite of 35 quality of life questions; lower scores indicate higher quality of life (range = -4 to 136). Nonmissing scores for items 27-33 imputed for patients who reported an impact due to COVID-19 pandemic. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

Alnylam Pharmaceuticals Inc.
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Table 3.7
Norfolk Quality of Life - Diabetic Neuropathy (QoL-DN) Total Score: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Baseline NIS: ≥50

Subgroup Visit	Vutrisiran (HELIOS-A) (N=44)	Patisiran (HELIOS-A) (N=15)
Month 18		
Actual Value		
n	39	12
Mean (SD)	67.0 (18.5)	66.8 (19.5)
SE	3.0	5.6
Median	66.0	64.5
Min, Max	18, 107	32, 99
Change from baseline		
n	39	12
Mean (SD)	3.1 (21.2)	3.6 (21.3)
SE	3.4	6.2
Median	4.0	-1.5
Min, Max	-43, 58	-30, 58

Norfolk QoL-DN score = composite of 35 quality of life questions; lower scores indicate higher quality of life (range = -4 to 136). Nonmissing scores for items 27-33 imputed for patients who reported an impact due to COVID-19 pandemic. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

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Table 3.7
Norfolk Quality of Life - Diabetic Neuropathy (QoL-DN) Total Score: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Previous Tetramer Stabilizer Use: Yes

Subgroup Visit	Vutrisiran (HELIOS-A) (N=75)	Patisiran (HELIOS-A) (N=33)
Baseline		
n	75	33
Mean (SD)	45.4 (25.0)	51.0 (30.8)
SE	2.9	5.4
Median	42.0	54.0
Min, Max	2, 104	1, 125
Month 9		
Actual Value		
n	74	32
Mean (SD)	43.4 (26.0)	48.8 (27.0)
SE	3.0	4.8
Median	41.5	45.5
Min, Max	0, 102	4, 115
Change from baseline		
n	74	32
Mean (SD)	-1.8 (17.8)	-1.2 (16.5)
SE	2.1	2.9
Median	-0.5	-4.5
Min, Max	-59, 52	-26, 54

Norfolk QoL-DN score = composite of 35 quality of life questions; lower scores indicate higher quality of life (range = -4 to 136). Nonmissing scores for items 27-33 imputed for patients who reported an impact due to COVID-19 pandemic. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

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Table 3.7
Norfolk Quality of Life - Diabetic Neuropathy (QoL-DN) Total Score: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Previous Tetramer Stabilizer Use: Yes

Subgroup Visit	Vutrisiran (HELIOS-A) (N=75)	Patisiran (HELIOS-A) (N=33)
Month 18		
Actual Value		
n	71	31
Mean (SD)	44.9 (27.6)	45.9 (25.7)
SE	3.3	4.6
Median	43.0	43.0
Min, Max	2, 107	8, 99
Change from baseline		
n	71	31
Mean (SD)	0.1 (19.8)	-1.6 (17.9)
SE	2.3	3.2
Median	-2.0	-2.0
Min, Max	-51, 58	-49, 58

Norfolk QoL-DN score = composite of 35 quality of life questions; lower scores indicate higher quality of life (range = -4 to 136). Nonmissing scores for items 27-33 imputed for patients who reported an impact due to COVID-19 pandemic. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 3.7
Norfolk Quality of Life - Diabetic Neuropathy (QoL-DN) Total Score: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Previous Tetramer Stabilizer Use: No

Subgroup Visit	Vutrisiran (HELIOS-A) (N=47)	Patisiran (HELIOS-A) (N=9)
Baseline		
n	46	9
Mean (SD)	49.9 (28.4)	33.8 (23.3)
SE	4.2	7.8
Median	46.0	32.0
Min, Max	-1, 105	5, 88
Month 9		
Actual Value		
n	42	8
Mean (SD)	38.2 (27.6)	36.0 (31.0)
SE	4.3	11.0
Median	34.5	31.5
Min, Max	-4, 87	1, 84
Change from baseline		
n	41	8
Mean (SD)	-8.7 (18.9)	1.6 (24.3)
SE	3.0	8.6
Median	-9.0	-6.5
Min, Max	-55, 39	-26, 43

Norfolk QoL-DN score = composite of 35 quality of life questions; lower scores indicate higher quality of life (range = -4 to 136). Nonmissing scores for items 27-33 imputed for patients who reported an impact due to COVID-19 pandemic. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 3.7
Norfolk Quality of Life - Diabetic Neuropathy (QoL-DN) Total Score: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Previous Tetramer Stabilizer Use: No

Subgroup Visit	Vutrisiran (HELIOS-A) (N=47)	Patisiran (HELIOS-A) (N=9)
Month 18		
Actual Value		
n	43	7
Mean (SD)	40.6 (26.6)	37.6 (35.0)
SE	4.1	13.2
Median	37.0	24.0
Min, Max	0, 96	1, 83
Change from baseline		
n	42	7
Mean (SD)	-6.6 (23.4)	3.9 (26.0)
SE	3.6	9.8
Median	-9.0	-4.0
Min, Max	-52, 67	-23, 40

Norfolk QoL-DN score = composite of 35 quality of life questions; lower scores indicate higher quality of life (range = -4 to 136). Nonmissing scores for items 27-33 imputed for patients who reported an impact due to COVID-19 pandemic. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 3.7
Norfolk Quality of Life - Diabetic Neuropathy (QoL-DN) Total Score: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Genotype: V30M

Subgroup Visit	Vutrisiran (HELIOS-A) (N=54)	Patisiran (HELIOS-A) (N=20)
Baseline		
n	53	20
Mean (SD)	46.9 (27.4)	52.7 (25.8)
SE	3.8	5.8
Median	42.0	52.5
Min, Max	-1, 104	17, 115
Month 9		
Actual Value		
n	52	20
Mean (SD)	40.6 (24.9)	47.7 (20.6)
SE	3.4	4.6
Median	40.0	45.5
Min, Max	0, 102	12, 90
Change from baseline		
n	51	20
Mean (SD)	-5.3 (16.1)	-5.0 (13.2)
SE	2.3	3.0
Median	-2.0	-7.5
Min, Max	-55, 28	-25, 17

Norfolk QoL-DN score = composite of 35 quality of life questions; lower scores indicate higher quality of life (range = -4 to 136). Nonmissing scores for items 27-33 imputed for patients who reported an impact due to COVID-19 pandemic. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 3.7
Norfolk Quality of Life - Diabetic Neuropathy (QoL-DN) Total Score: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Genotype: V30M

Subgroup Visit	Vutrisiran (HELIOS-A) (N=54)	Patisiran (HELIOS-A) (N=20)
Month 18		
Actual Value		
n	52	20
Mean (SD)	41.5 (25.9)	49.0 (22.5)
SE	3.6	5.0
Median	42.0	52.5
Min, Max	2, 94	10, 85
Change from baseline		
n	51	20
Mean (SD)	-3.8 (19.7)	-3.8 (13.9)
SE	2.8	3.1
Median	-5.0	-3.5
Min, Max	-52, 34	-30, 38

Norfolk QoL-DN score = composite of 35 quality of life questions; lower scores indicate higher quality of life (range = -4 to 136). Nonmissing scores for items 27-33 imputed for patients who reported an impact due to COVID-19 pandemic. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 3.7
Norfolk Quality of Life - Diabetic Neuropathy (QoL-DN) Total Score: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Genotype: non-V30M

Subgroup Visit	Vutrisiran (HELIOS-A) (N=68)	Patisiran (HELIOS-A) (N=22)
Baseline		
n	68	22
Mean (SD)	47.3 (25.7)	42.5 (33.1)
SE	3.1	7.1
Median	45.0	36.0
Min, Max	3, 105	1, 125
Month 9		
Actual Value		
n	64	20
Mean (SD)	42.2 (28.1)	44.7 (34.2)
SE	3.5	7.6
Median	39.5	33.5
Min, Max	-4, 97	1, 115
Change from baseline		
n	64	20
Mean (SD)	-3.5 (20.2)	3.8 (21.2)
SE	2.5	4.7
Median	-3.0	2.0
Min, Max	-59, 52	-26, 54

Norfolk QoL-DN score = composite of 35 quality of life questions; lower scores indicate higher quality of life (range = -4 to 136). Nonmissing scores for items 27-33 imputed for patients who reported an impact due to COVID-19 pandemic. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

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Table 3.7
Norfolk Quality of Life - Diabetic Neuropathy (QoL-DN) Total Score: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Genotype: non-V30M

Subgroup Visit	Vutrisiran (HELIOS-A) (N=68)	Patisiran (HELIOS-A) (N=22)
Month 18		
Actual Value		
n	62	18
Mean (SD)	44.7 (28.4)	39.3 (31.6)
SE	3.6	7.5
Median	42.0	28.5
Min, Max	0, 107	1, 99
Change from baseline		
n	62	18
Mean (SD)	-1.2 (22.7)	2.9 (23.9)
SE	2.9	5.6
Median	-2.0	3.5
Min, Max	-45, 67	-49, 58

Norfolk QoL-DN score = composite of 35 quality of life questions; lower scores indicate higher quality of life (range = -4 to 136). Nonmissing scores for items 27-33 imputed for patients who reported an impact due to COVID-19 pandemic. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 3.7
Norfolk Quality of Life - Diabetic Neuropathy (QoL-DN) Total Score: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

FAP Stage: I

Subgroup Visit	Vutrisiran (HELIOS-A) (N=84)	Patisiran (HELIOS-A) (N=31)
Baseline		
n	83	31
Mean (SD)	40.4 (24.5)	39.4 (26.5)
SE	2.7	4.8
Median	37.0	34.0
Min, Max	-1, 95	1, 88
Month 9		
Actual Value		
n	82	30
Mean (SD)	33.1 (22.1)	37.6 (22.7)
SE	2.4	4.1
Median	28.5	36.0
Min, Max	-4, 83	1, 79
Change from baseline		
n	81	30
Mean (SD)	-6.4 (17.9)	-2.1 (14.1)
SE	2.0	2.6
Median	-6.0	-4.5
Min, Max	-59, 41	-26, 26

Norfolk QoL-DN score = composite of 35 quality of life questions; lower scores indicate higher quality of life (range = -4 to 136). Nonmissing scores for items 27-33 imputed for patients who reported an impact due to COVID-19 pandemic. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 3.7
Norfolk Quality of Life - Diabetic Neuropathy (QoL-DN) Total Score: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

FAP Stage: I

Subgroup Visit	Vutrisiran (HELIOS-A) (N=84)	Patisiran (HELIOS-A) (N=31)
Month 18		
Actual Value		
n	81	30
Mean (SD)	34.7 (24.0)	36.3 (24.0)
SE	2.7	4.4
Median	28.0	32.0
Min, Max	0, 89	1, 83
Change from baseline		
n	80	30
Mean (SD)	-4.2 (19.8)	-3.5 (15.9)
SE	2.2	2.9
Median	-6.0	-3.0
Min, Max	-52, 44	-49, 38

Norfolk QoL-DN score = composite of 35 quality of life questions; lower scores indicate higher quality of life (range = -4 to 136). Nonmissing scores for items 27-33 imputed for patients who reported an impact due to COVID-19 pandemic. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 3.7
Norfolk Quality of Life - Diabetic Neuropathy (QoL-DN) Total Score: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

FAP Stage: II&III

Subgroup Visit	Vutrisiran (HELIOS-A) (N=38)	Patisiran (HELIOS-A) (N=11)
Baseline		
n	38	11
Mean (SD)	61.8 (24.4)	69.6 (28.8)
SE	4.0	8.7
Median	64.5	65.0
Min, Max	17, 105	39, 125
Month 9		
Actual Value		
n	34	10
Mean (SD)	61.9 (25.5)	71.9 (27.2)
SE	4.4	8.6
Median	69.0	77.5
Min, Max	5, 102	30, 115
Change from baseline		
n	34	10
Mean (SD)	0.9 (19.0)	3.9 (27.2)
SE	3.3	8.6
Median	1.5	-3.5
Min, Max	-40, 52	-25, 54

Norfolk QoL-DN score = composite of 35 quality of life questions; lower scores indicate higher quality of life (range = -4 to 136). Nonmissing scores for items 27-33 imputed for patients who reported an impact due to COVID-19 pandemic. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 3.7
Norfolk Quality of Life - Diabetic Neuropathy (QoL-DN) Total Score: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

FAP Stage: II&III

Subgroup Visit	Vutrisiran (HELIOS-A) (N=38)	Patisiran (HELIOS-A) (N=11)
Month 18		
Actual Value		
n	33	8
Mean (SD)	64.3 (23.0)	74.6 (14.6)
SE	4.0	5.2
Median	66.0	73.5
Min, Max	7, 107	59, 99
Change from baseline		
n	33	8
Mean (SD)	2.0 (24.5)	10.1 (27.5)
SE	4.3	9.7
Median	-1.0	4.0
Min, Max	-51, 67	-30, 58

Norfolk QoL-DN score = composite of 35 quality of life questions; lower scores indicate higher quality of life (range = -4 to 136). Nonmissing scores for items 27-33 imputed for patients who reported an impact due to COVID-19 pandemic. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 3.7
Norfolk Quality of Life - Diabetic Neuropathy (QoL-DN) Total Score: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Cardiac Subpopulation: Yes

Subgroup Visit	Vutrisiran (HELIOS-A) (N=40)	Patisiran (HELIOS-A) (N=14)
Baseline		
n	40	14
Mean (SD)	53.4 (26.2)	57.8 (39.6)
SE	4.1	10.6
Median	47.0	65.5
Min, Max	14, 105	1, 125
Month 9		
Actual Value		
n	38	14
Mean (SD)	47.4 (27.6)	61.8 (34.0)
SE	4.5	9.1
Median	42.0	73.0
Min, Max	7, 102	4, 115
Change from baseline		
n	38	14
Mean (SD)	-5.0 (20.5)	4.0 (22.8)
SE	3.3	6.1
Median	-3.5	-1.0
Min, Max	-59, 52	-25, 54

Norfolk QoL-DN score = composite of 35 quality of life questions; lower scores indicate higher quality of life (range = -4 to 136). Nonmissing scores for items 27-33 imputed for patients who reported an impact due to COVID-19 pandemic. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 3.7
Norfolk Quality of Life - Diabetic Neuropathy (QoL-DN) Total Score: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Cardiac Subpopulation: Yes

Subgroup Visit	Vutrisiran (HELIOS-A) (N=40)	Patisiran (HELIOS-A) (N=14)
Month 18		
Actual Value		
n	37	13
Mean (SD)	50.1 (29.8)	59.3 (31.1)
SE	4.9	8.6
Median	44.0	76.0
Min, Max	2, 107	10, 99
Change from baseline		
n	37	13
Mean (SD)	-2.8 (23.7)	6.7 (24.3)
SE	3.9	6.7
Median	-7.0	9.0
Min, Max	-51, 58	-30, 58

Norfolk QoL-DN score = composite of 35 quality of life questions; lower scores indicate higher quality of life (range = -4 to 136). Nonmissing scores for items 27-33 imputed for patients who reported an impact due to COVID-19 pandemic. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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ALN-TTRSC02-002

Table 3.7
Norfolk Quality of Life - Diabetic Neuropathy (QoL-DN) Total Score: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Cardiac Subpopulation: No

Subgroup Visit	Vutrisiran (HELIOS-A) (N=82)	Patisiran (HELIOS-A) (N=28)
Baseline		
n	81	28
Mean (SD)	44.0 (26.0)	42.1 (22.8)
SE	2.9	4.3
Median	42.0	39.5
Min, Max	-1, 102	5, 88
Month 9		
Actual Value		
n	78	26
Mean (SD)	38.7 (25.8)	37.8 (20.1)
SE	2.9	3.9
Median	38.5	36.0
Min, Max	-4, 89	1, 76
Change from baseline		
n	77	26
Mean (SD)	-3.9 (17.4)	-3.1 (14.7)
SE	2.0	2.9
Median	-2.0	-6.0
Min, Max	-55, 41	-26, 26

Norfolk QoL-DN score = composite of 35 quality of life questions; lower scores indicate higher quality of life (range = -4 to 136). Nonmissing scores for items 27-33 imputed for patients who reported an impact due to COVID-19 pandemic. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 3.7
Norfolk Quality of Life - Diabetic Neuropathy (QoL-DN) Total Score: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Cardiac Subpopulation: No

Subgroup Visit	Vutrisiran (HELIOS-A) (N=82)	Patisiran (HELIOS-A) (N=28)
Month 18		
Actual Value		
n	77	25
Mean (SD)	39.9 (25.4)	36.6 (21.9)
SE	2.9	4.4
Median	41.0	34.0
Min, Max	0, 89	1, 83
Change from baseline		
n	76	25
Mean (SD)	-2.2 (20.2)	-4.4 (15.4)
SE	2.3	3.1
Median	-3.0	-2.0
Min, Max	-52, 67	-49, 38

Norfolk QoL-DN score = composite of 35 quality of life questions; lower scores indicate higher quality of life (range = -4 to 136). Nonmissing scores for items 27-33 imputed for patients who reported an impact due to COVID-19 pandemic. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 3.7
Norfolk Quality of Life - Diabetic Neuropathy (QoL-DN) Total Score: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Weight (kg): <65

Subgroup Visit	Vutrisiran (HELIOS-A) (N=46)	Patisiran (HELIOS-A) (N=15)
Baseline		
n	46	15
Mean (SD)	50.0 (27.2)	48.4 (31.2)
SE	4.0	8.0
Median	48.5	51.0
Min, Max	2, 105	10, 115
Month 9		
Actual Value		
n	44	15
Mean (SD)	45.8 (26.0)	45.0 (21.1)
SE	3.9	5.4
Median	42.0	36.0
Min, Max	0, 102	12, 90
Change from baseline		
n	44	15
Mean (SD)	-3.2 (21.0)	-3.4 (17.5)
SE	3.2	4.5
Median	-2.0	-8.0
Min, Max	-55, 52	-26, 26

Norfolk QoL-DN score = composite of 35 quality of life questions; lower scores indicate higher quality of life (range = -4 to 136). Nonmissing scores for items 27-33 imputed for patients who reported an impact due to COVID-19 pandemic. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 3.7
Norfolk Quality of Life - Diabetic Neuropathy (QoL-DN) Total Score: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Weight (kg): <65

Subgroup Visit	Vutrisiran (HELIOS-A) (N=46)	Patisiran (HELIOS-A) (N=15)
Month 18		
Actual Value		
n	42	15
Mean (SD)	47.3 (27.1)	47.9 (24.1)
SE	4.2	6.2
Median	50.0	40.0
Min, Max	2, 96	10, 85
Change from baseline		
n	42	15
Mean (SD)	-1.3 (21.5)	-0.5 (15.8)
SE	3.3	4.1
Median	0.5	-2.0
Min, Max	-51, 58	-30, 38

Norfolk QoL-DN score = composite of 35 quality of life questions; lower scores indicate higher quality of life (range = -4 to 136). Nonmissing scores for items 27-33 imputed for patients who reported an impact due to COVID-19 pandemic. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 3.7
Norfolk Quality of Life - Diabetic Neuropathy (QoL-DN) Total Score: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Weight (kg): ≥65

Subgroup Visit	Vutrisiran (HELIOS-A) (N=76)	Patisiran (HELIOS-A) (N=27)
Baseline		
n	75	27
Mean (SD)	45.4 (25.8)	46.7 (29.8)
SE	3.0	5.7
Median	42.0	41.0
Min, Max	-1, 102	1, 125
Month 9		
Actual Value		
n	72	25
Mean (SD)	38.9 (26.7)	46.9 (31.7)
SE	3.2	6.3
Median	38.5	48.0
Min, Max	-4, 97	1, 115
Change from baseline		
n	71	25
Mean (SD)	-4.9 (16.8)	1.0 (18.4)
SE	2.0	3.7
Median	-4.0	-3.0
Min, Max	-59, 41	-26, 54

Norfolk QoL-DN score = composite of 35 quality of life questions; lower scores indicate higher quality of life (range = -4 to 136). Nonmissing scores for items 27-33 imputed for patients who reported an impact due to COVID-19 pandemic. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 3.7
Norfolk Quality of Life - Diabetic Neuropathy (QoL-DN) Total Score: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Weight (kg): ≥65

Subgroup Visit	Vutrisiran (HELIOS-A) (N=76)	Patisiran (HELIOS-A) (N=27)
Month 18		
Actual Value		
n	72	23
Mean (SD)	40.9 (27.2)	42.1 (29.4)
SE	3.2	6.1
Median	37.0	43.0
Min, Max	0, 107	1, 99
Change from baseline		
n	71	23
Mean (SD)	-3.1 (21.4)	-0.7 (21.7)
SE	2.5	4.5
Median	-7.0	-2.0
Min, Max	-52, 67	-49, 58

Norfolk QoL-DN score = composite of 35 quality of life questions; lower scores indicate higher quality of life (range = -4 to 136). Nonmissing scores for items 27-33 imputed for patients who reported an impact due to COVID-19 pandemic. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Norfolk-QoL-DN-Gesamtwert (Binäre Analyse)

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Table 3.6
Norfolk Quality of Life - Diabetic Neuropathy (QoL-DN) Total Score: Binary Subgroup Analysis
mITT Population

Month 9

Analysis Visit Statistics	Vutrisiran (HELIOS-A) (N=122)	Patisiran (HELIOS-A) (N=42)
Age (years)		
<65		
Patients included in analysis, N1	76	31
<0 point increase from baseline, n(%)	41 (53.9)	18 (58.1)
≥0 point increase from baseline, n(%)	32 (42.1)	12 (38.7)
Missing, n(%)	3 (3.9)	1 (3.2)
<0 point increase from baseline, (95% CI)	53.9 (42.7, 65.2)	58.1 (40.7, 75.4)
Percentage difference (Vutrisiran – Patisiran), (95% CI)	-4.117 (-24.789, 16.554)	
Odds ratio (Vutrisiran/Patisiran), (95% CI) [1]	0.846 (0.364, 1.968)	
Relative risk (Vutrisiran/Patisiran), (95% CI) [1]	0.929 (0.645, 1.337)	
P-value [2]	0.6923	

N1 = Patients with missing postbaseline values due to COVID-19 or after initiation of local standard treatment for hATTR amyloidosis were included in analysis.
[1] Based on unstratified analysis.
In estimation of the odds ratio and relative risk, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the percentage difference or p-value.
[2] p-value based on the Wald test testing whether the relative risk equals to 1.
[3] p-value from a logistic regression using the penalized likelihood estimation (the FIRTH option) and with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Table 3.6
Norfolk Quality of Life - Diabetic Neuropathy (QoL-DN) Total Score: Binary Subgroup Analysis
mITT Population

Month 9

Analysis Visit Statistics	Vutrisiran (HELIOS-A) (N=122)	Patisiran (HELIOS-A) (N=42)
≥65		
Patients included in analysis, N1	46	11
<0 point increase from baseline, n(%)	23 (50.0)	5 (45.5)
≥0 point increase from baseline, n(%)	19 (41.3)	5 (45.5)
Missing, n(%)	4 (8.7)	1 (9.1)
<0 point increase from baseline, (95% CI)	50.0 (35.6, 64.4)	45.5 (16.0, 74.9)
Percentage difference (Vutrisiran – Patisiran), (95% CI)	4.545 (-28.236, 37.327)	
Odds ratio (Vutrisiran/Patisiran), (95% CI) [1]	1.200 (0.321, 4.492)	
Relative risk (Vutrisiran/Patisiran), (95% CI) [1]	1.100 (0.541, 2.235)	
P-value [2]	0.7922	
p-value of Treatment*Age [3]	0.6831	

N1 = Patients with missing postbaseline values due to COVID-19 or after initiation of local standard treatment for hATTR amyloidosis were included in analysis.
[1] Based on unstratified analysis.
In estimation of the odds ratio and relative risk, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the percentage difference or p-value.
[2] p-value based on the Wald test testing whether the relative risk equals to 1.
[3] p-value from a logistic regression using the penalized likelihood estimation (the FIRTH option) and with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Table 3.6
Norfolk Quality of Life - Diabetic Neuropathy (QoL-DN) Total Score: Binary Subgroup Analysis
mITT Population

Month 18

Analysis Visit Statistics	Vutrisiran (HELIOS-A) (N=122)	Patisiran (HELIOS-A) (N=42)
Age (years)		
<65		
Patients included in analysis, N1	76	31
<0 point increase from baseline, n(%)	47 (61.8)	16 (51.6)
≥0 point increase from baseline, n(%)	26 (34.2)	13 (41.9)
Missing, n(%)	3 (3.9)	2 (6.5)
<0 point increase from baseline, (95% CI)	61.8 (50.9, 72.8)	51.6 (34.0, 69.2)
Percentage difference (Vutrisiran − Patisiran), (95% CI)	10.229 (-10.477, 30.935)	
Odds ratio (Vutrisiran/Patisiran), (95% CI) [1]	1.519 (0.654, 3.530)	
Relative risk (Vutrisiran/Patisiran), (95% CI) [1]	1.198 (0.816, 1.759)	
P-value [2]	0.3559	

N1 = Patients with missing postbaseline values due to COVID-19 or after initiation of local standard treatment for hATTR amyloidosis were included in analysis.
[1] Based on unstratified analysis.
In estimation of the odds ratio and relative risk, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the percentage difference or p-value.
[2] p-value based on the Wald test testing whether the relative risk equals to 1.
[3] p-value from a logistic regression using the penalized likelihood estimation (the FIRTH option) and with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Table 3.6
Norfolk Quality of Life - Diabetic Neuropathy (QoL-DN) Total Score: Binary Subgroup Analysis
mITT Population

Month 18

Analysis Visit Statistics	Vutrisiran (HELIOS-A) (N=122)	Patisiran (HELIOS-A) (N=42)
≥65		
Patients included in analysis, N1	46	11
<0 point increase from baseline, n(%)	21 (45.7)	5 (45.5)
≥0 point increase from baseline, n(%)	19 (41.3)	4 (36.4)
Missing, n(%)	6 (13.0)	2 (18.2)
<0 point increase from baseline, (95% CI)	45.7 (31.3, 60.0)	45.5 (16.0, 74.9)
Percentage difference (Vutrisiran – Patisiran), (95% CI)	0.198 (-32.560, 32.955)	
Odds ratio (Vutrisiran/Patisiran), (95% CI) [1]	1.008 (0.269, 3.777)	
Relative risk (Vutrisiran/Patisiran), (95% CI) [1]	1.004 (0.489, 2.063)	
P-value [2]	0.9906	
p-value of Treatment*Age [3]	0.6017	

N1 = Patients with missing postbaseline values due to COVID-19 or after initiation of local standard treatment for hATTR amyloidosis were included in analysis.
[1] Based on unstratified analysis.
In estimation of the odds ratio and relative risk, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the percentage difference or p-value.
[2] p-value based on the Wald test testing whether the relative risk equals to 1.
[3] p-value from a logistic regression using the penalized likelihood estimation (the FIRTH option) and with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Table 3.6
Norfolk Quality of Life - Diabetic Neuropathy (QoL-DN) Total Score: Binary Subgroup Analysis
mITT Population

Month 9

Analysis Visit Statistics	Vutrisiran (HELIOS-A) (N=122)	Patisiran (HELIOS-A) (N=42)
Sex		
Male		
Patients included in analysis, N1	79	27
<0 point increase from baseline, n(%)	41 (51.9)	14 (51.9)
≥0 point increase from baseline, n(%)	34 (43.0)	11 (40.7)
Missing, n(%)	4 (5.1)	2 (7.4)
<0 point increase from baseline, (95% CI)	51.9 (40.9, 62.9)	51.9 (33.0, 70.7)
Percentage difference (Vutrisiran − Patisiran), (95% CI)	0.047 (-21.784, 21.878)	
Odds ratio (Vutrisiran/Patisiran), (95% CI) [1]	1.002 (0.418, 2.402)	
Relative risk (Vutrisiran/Patisiran), (95% CI) [1]	1.001 (0.657, 1.525)	
P-value [2]	0.9966	

N1 = Patients with missing postbaseline values due to COVID-19 or after initiation of local standard treatment for hATTR amyloidosis were included in analysis.
[1] Based on unstratified analysis.
In estimation of the odds ratio and relative risk, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the percentage difference or p-value.
[2] p-value based on the Wald test testing whether the relative risk equals to 1.
[3] p-value from a logistic regression using the penalized likelihood estimation (the FIRTH option) and with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Table 3.6
Norfolk Quality of Life - Diabetic Neuropathy (QoL-DN) Total Score: Binary Subgroup Analysis
mITT Population

Month 9

Analysis Visit Statistics	Vutrisiran (HELIOS-A) (N=122)	Patisiran (HELIOS-A) (N=42)
Female		
Patients included in analysis, N1	43	15
<0 point increase from baseline, n(%)	23 (53.5)	9 (60.0)
≥0 point increase from baseline, n(%)	17 (39.5)	6 (40.0)
Missing, n(%)	3 (7.0)	0
<0 point increase from baseline, (95% CI)	53.5 (38.6, 68.4)	60.0 (35.2, 84.8)
Percentage difference (Vutrisiran – Patisiran), (95% CI)	-6.512 (-35.441, 22.417)	
Odds ratio (Vutrisiran/Patisiran), (95% CI) [1]	0.767 (0.232, 2.531)	
Relative risk (Vutrisiran/Patisiran), (95% CI) [1]	0.891 (0.542, 1.467)	
P-value [2]	0.6514	
p-value of Treatment*Sex [3]	0.7438	

N1 = Patients with missing postbaseline values due to COVID-19 or after initiation of local standard treatment for hATTR amyloidosis were included in analysis.
[1] Based on unstratified analysis.
In estimation of the odds ratio and relative risk, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the percentage difference or p-value.
[2] p-value based on the Wald test testing whether the relative risk equals to 1.
[3] p-value from a logistic regression using the penalized likelihood estimation (the FIRTH option) and with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Table 3.6
Norfolk Quality of Life - Diabetic Neuropathy (QoL-DN) Total Score: Binary Subgroup Analysis
mITT Population

Month 18

Analysis Visit Statistics	Vutrisiran (HELIOS-A) (N=122)	Patisiran (HELIOS-A) (N=42)
Sex		
Male		
Patients included in analysis, N1	79	27
<0 point increase from baseline, n(%)	43 (54.4)	13 (48.1)
≥0 point increase from baseline, n(%)	30 (38.0)	10 (37.0)
Missing, n(%)	6 (7.6)	4 (14.8)
<0 point increase from baseline, (95% CI)	54.4 (43.4, 65.4)	48.1 (29.3, 67.0)
Percentage difference (Vutrisiran – Patisiran), (95% CI)	6.282 (-15.531, 28.095)	
Odds ratio (Vutrisiran/Patisiran), (95% CI) [1]	1.286 (0.536, 3.086)	
Relative risk (Vutrisiran/Patisiran), (95% CI) [1]	1.130 (0.728, 1.756)	
P-value [2]	0.5852	

N1 = Patients with missing postbaseline values due to COVID-19 or after initiation of local standard treatment for hATTR amyloidosis were included in analysis.
[1] Based on unstratified analysis.
In estimation of the odds ratio and relative risk, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the percentage difference or p-value.
[2] p-value based on the Wald test testing whether the relative risk equals to 1.
[3] p-value from a logistic regression using the penalized likelihood estimation (the FIRTH option) and with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Table 3.6
Norfolk Quality of Life - Diabetic Neuropathy (QoL-DN) Total Score: Binary Subgroup Analysis
mITT Population

Month 18

Analysis Visit Statistics	Vutrisiran (HELIOS-A) (N=122)	Patisiran (HELIOS-A) (N=42)
Female		
Patients included in analysis, N1	43	15
<0 point increase from baseline, n(%)	25 (58.1)	8 (53.3)
≥0 point increase from baseline, n(%)	15 (34.9)	7 (46.7)
Missing, n(%)	3 (7.0)	0
<0 point increase from baseline, (95% CI)	58.1 (43.4, 72.9)	53.3 (28.1, 78.6)
Percentage difference (Vutrisiran – Patisiran), (95% CI)	4.806 (-24.431, 34.043)	
Odds ratio (Vutrisiran/Patisiran), (95% CI) [1]	1.215 (0.373, 3.961)	
Relative risk (Vutrisiran/Patisiran), (95% CI) [1]	1.090 (0.637, 1.865)	
P-value [2]	0.7528	
p-value of Treatment*Sex [3]	0.9456	

N1 = Patients with missing postbaseline values due to COVID-19 or after initiation of local standard treatment for hATTR amyloidosis were included in analysis.
[1] Based on unstratified analysis.
In estimation of the odds ratio and relative risk, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the percentage difference or p-value.
[2] p-value based on the Wald test testing whether the relative risk equals to 1.
[3] p-value from a logistic regression using the penalized likelihood estimation (the FIRTH option) and with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Table 3.6
Norfolk Quality of Life - Diabetic Neuropathy (QoL-DN) Total Score: Binary Subgroup Analysis
mITT Population

Month 9

Analysis Visit Statistics	Vutrisiran (HELIOS-A) (N=122)	Patisiran (HELIOS-A) (N=42)
Race		
White		
Patients included in analysis, N1	86	29
<0 point increase from baseline, n(%)	41 (47.7)	17 (58.6)
≥0 point increase from baseline, n(%)	40 (46.5)	11 (37.9)
Missing, n(%)	5 (5.8)	1 (3.4)
<0 point increase from baseline, (95% CI)	47.7 (37.1, 58.2)	58.6 (40.7, 76.5)
Percentage difference (Vutrisiran – Patisiran), (95% CI)	-10.946 (-31.749, 9.856)	
Odds ratio (Vutrisiran/Patisiran), (95% CI) [1]	0.643 (0.274, 1.507)	
Relative risk (Vutrisiran/Patisiran), (95% CI) [1]	0.813 (0.558, 1.186)	
P-value [2]	0.2832	

N1 = Patients with missing postbaseline values due to COVID-19 or after initiation of local standard treatment for hATTR amyloidosis were included in analysis.
[1] Based on unstratified analysis.
In estimation of the odds ratio and relative risk, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the percentage difference or p-value.
[2] p-value based on the Wald test testing whether the relative risk equals to 1.
[3] p-value from a logistic regression using the penalized likelihood estimation (the FIRTH option) and with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Table 3.6
Norfolk Quality of Life - Diabetic Neuropathy (QoL-DN) Total Score: Binary Subgroup Analysis
mITT Population

Month 9

Analysis Visit Statistics	Vutrisiran (HELIOS-A) (N=122)	Patisiran (HELIOS-A) (N=42)
All Other Races		
Patients included in analysis, N1	36	13
<0 point increase from baseline, n(%)	23 (63.9)	6 (46.2)
≥0 point increase from baseline, n(%)	11 (30.6)	6 (46.2)
Missing, n(%)	2 (5.6)	1 (7.7)
<0 point increase from baseline, (95% CI)	63.9 (48.2, 79.6)	46.2 (19.1, 73.3)
Percentage difference (Vutrisiran – Patisiran), (95% CI)	17.735 (-13.579, 49.049)	
Odds ratio (Vutrisiran/Patisiran), (95% CI) [1]	2.064 (0.571, 7.462)	
Relative risk (Vutrisiran/Patisiran), (95% CI) [1]	1.384 (0.733, 2.616)	
P-value [2]	0.3166	
p-value of Treatment*Race [3]	0.1519	

N1 = Patients with missing postbaseline values due to COVID-19 or after initiation of local standard treatment for hATTR amyloidosis were included in analysis.
[1] Based on unstratified analysis.
In estimation of the odds ratio and relative risk, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the percentage difference or p-value.
[2] p-value based on the Wald test testing whether the relative risk equals to 1.
[3] p-value from a logistic regression using the penalized likelihood estimation (the FIRTH option) and with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Table 3.6
Norfolk Quality of Life - Diabetic Neuropathy (QoL-DN) Total Score: Binary Subgroup Analysis
mITT Population

Month 18

Analysis Visit Statistics	Vutrisiran (HELIOS-A) (N=122)	Patisiran (HELIOS-A) (N=42)
Race		
White		
Patients included in analysis, N1	86	29
<0 point increase from baseline, n(%)	48 (55.8)	16 (55.2)
≥0 point increase from baseline, n(%)	32 (37.2)	11 (37.9)
Missing, n(%)	6 (7.0)	2 (6.9)
<0 point increase from baseline, (95% CI)	55.8 (45.3, 66.3)	55.2 (37.1, 73.3)
Percentage difference (Vutrisiran – Patisiran), (95% CI)	0.642 (-20.282, 21.565)	
Odds ratio (Vutrisiran/Patisiran), (95% CI) [1]	1.026 (0.440, 2.393)	
Relative risk (Vutrisiran/Patisiran), (95% CI) [1]	1.012 (0.693, 1.477)	
P-value [2]	0.9522	

N1 = Patients with missing postbaseline values due to COVID-19 or after initiation of local standard treatment for hATTR amyloidosis were included in analysis.
[1] Based on unstratified analysis.
In estimation of the odds ratio and relative risk, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the percentage difference or p-value.
[2] p-value based on the Wald test testing whether the relative risk equals to 1.
[3] p-value from a logistic regression using the penalized likelihood estimation (the FIRTH option) and with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Table 3.6
Norfolk Quality of Life - Diabetic Neuropathy (QoL-DN) Total Score: Binary Subgroup Analysis
mITT Population

Month 18

Analysis Visit Statistics	Vutrisiran (HELIOS-A) (N=122)	Patisiran (HELIOS-A) (N=42)
All Other Races		
Patients included in analysis, N1	36	13
<0 point increase from baseline, n(%)	20 (55.6)	5 (38.5)
≥0 point increase from baseline, n(%)	13 (36.1)	6 (46.2)
Missing, n(%)	3 (8.3)	2 (15.4)
<0 point increase from baseline, (95% CI)	55.6 (39.3, 71.8)	38.5 (12.0, 64.9)
Percentage difference (Vutrisiran – Patisiran), (95% CI)	17.094 (-13.936, 48.124)	
Odds ratio (Vutrisiran/Patisiran), (95% CI) [1]	2.000 (0.547, 7.312)	
Relative risk (Vutrisiran/Patisiran), (95% CI) [1]	1.444 (0.684, 3.049)	
P-value [2]	0.3347	
p-value of Treatment*Race [3]	0.4298	

N1 = Patients with missing postbaseline values due to COVID-19 or after initiation of local standard treatment for hATTR amyloidosis were included in analysis.
[1] Based on unstratified analysis.
In estimation of the odds ratio and relative risk, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the percentage difference or p-value.
[2] p-value based on the Wald test testing whether the relative risk equals to 1.
[3] p-value from a logistic regression using the penalized likelihood estimation (the FIRTH option) and with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Table 3.6
Norfolk Quality of Life - Diabetic Neuropathy (QoL-DN) Total Score: Binary Subgroup Analysis
mITT Population

Month 9

Analysis Visit Statistics	Vutrisiran (HELIOS-A) (N=122)	Patisiran (HELIOS-A) (N=42)
Region		
North America		
Patients included in analysis, N1	27	8
<0 point increase from baseline, n(%)	13 (48.1)	5 (62.5)
≥0 point increase from baseline, n(%)	11 (40.7)	3 (37.5)
Missing, n(%)	3 (11.1)	0
<0 point increase from baseline, (95% CI)	48.1 (29.3, 67.0)	62.5 (29.0, 96.0)
Percentage difference (Vutrisiran – Patisiran), (95% CI)	-14.352 (-52.831, 24.127)	
Odds ratio (Vutrisiran/Patisiran), (95% CI) [1]	0.557 (0.110, 2.810)	
Relative risk (Vutrisiran/Patisiran), (95% CI) [1]	0.770 (0.396, 1.497)	
P-value [2]	0.4415	

N1 = Patients with missing postbaseline values due to COVID-19 or after initiation of local standard treatment for hATTR amyloidosis were included in analysis.
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In estimation of the odds ratio and relative risk, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the percentage difference or p-value.
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[3] p-value from a logistic regression using the penalized likelihood estimation (the FIRTH option) and with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Table 3.6
Norfolk Quality of Life - Diabetic Neuropathy (QoL-DN) Total Score: Binary Subgroup Analysis
mITT Population

Month 9

Analysis Visit Statistics	Vutrisiran (HELIOS-A) (N=122)	Patisiran (HELIOS-A) (N=42)
Western Europe		
Patients included in analysis, N1	42	20
<0 point increase from baseline, n(%)	23 (54.8)	12 (60.0)
≥0 point increase from baseline, n(%)	16 (38.1)	6 (30.0)
Missing, n(%)	3 (7.1)	2 (10.0)
<0 point increase from baseline, (95% CI)	54.8 (39.7, 69.8)	60.0 (38.5, 81.5)
Percentage difference (Vutrisiran – Patisiran), (95% CI)	-5.238 (-31.459, 20.983)	
Odds ratio (Vutrisiran/Patisiran), (95% CI) [1]	0.807 (0.274, 2.380)	
Relative risk (Vutrisiran/Patisiran), (95% CI) [1]	0.913 (0.581, 1.433)	
P-value [2]	0.6915	

N1 = Patients with missing postbaseline values due to COVID-19 or after initiation of local standard treatment for hATTR amyloidosis were included in analysis.
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In estimation of the odds ratio and relative risk, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the percentage difference or p-value.
[2] p-value based on the Wald test testing whether the relative risk equals to 1.
[3] p-value from a logistic regression using the penalized likelihood estimation (the FIRTH option) and with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Table 3.6
Norfolk Quality of Life - Diabetic Neuropathy (QoL-DN) Total Score: Binary Subgroup Analysis
mITT Population

Month 9

Analysis Visit Statistics	Vutrisiran (HELIOS-A) (N=122)	Patisiran (HELIOS-A) (N=42)
Rest of World		
Patients included in analysis, N1	53	14
<0 point increase from baseline, n(%)	28 (52.8)	6 (42.9)
≥0 point increase from baseline, n(%)	24 (45.3)	8 (57.1)
Missing, n(%)	1 (1.9)	0
<0 point increase from baseline, (95% CI)	52.8 (39.4, 66.3)	42.9 (16.9, 68.8)
Percentage difference (Vutrisiran – Patisiran), (95% CI)	9.973 (-19.226, 39.172)	
Odds ratio (Vutrisiran/Patisiran), (95% CI) [1]	1.493 (0.455, 4.899)	
Relative risk (Vutrisiran/Patisiran), (95% CI) [1]	1.233 (0.640, 2.376)	
P-value [2]	0.5320	
p-value of Treatment*Region [3]	0.6345	

N1 = Patients with missing postbaseline values due to COVID-19 or after initiation of local standard treatment for hATTR amyloidosis were included in analysis.
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[2] p-value based on the Wald test testing whether the relative risk equals to 1.
[3] p-value from a logistic regression using the penalized likelihood estimation (the FIRTH option) and with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Table 3.6
Norfolk Quality of Life - Diabetic Neuropathy (QoL-DN) Total Score: Binary Subgroup Analysis
mITT Population

Month 18

Analysis Visit Statistics	Vutrisiran (HELIOS-A) (N=122)	Patisiran (HELIOS-A) (N=42)
Region		
North America		
Patients included in analysis, N1	27	8
<0 point increase from baseline, n(%)	14 (51.9)	4 (50.0)
≥0 point increase from baseline, n(%)	10 (37.0)	3 (37.5)
Missing, n(%)	3 (11.1)	1 (12.5)
<0 point increase from baseline, (95% CI)	51.9 (33.0, 70.7)	50.0 (15.4, 84.6)
Percentage difference (Vutrisiran – Patisiran), (95% CI)	1.852 (-37.590, 41.294)	
Odds ratio (Vutrisiran/Patisiran), (95% CI) [1]	1.077 (0.222, 5.219)	
Relative risk (Vutrisiran/Patisiran), (95% CI) [1]	1.037 (0.474, 2.268)	
P-value [2]	0.9274	

N1 = Patients with missing postbaseline values due to COVID-19 or after initiation of local standard treatment for hATTR amyloidosis were included in analysis.
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In estimation of the odds ratio and relative risk, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the percentage difference or p-value.
[2] p-value based on the Wald test testing whether the relative risk equals to 1.
[3] p-value from a logistic regression using the penalized likelihood estimation (the FIRTH option) and with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Table 3.6
Norfolk Quality of Life - Diabetic Neuropathy (QoL-DN) Total Score: Binary Subgroup Analysis
mITT Population

Month 18

Analysis Visit Statistics	Vutrisiran (HELIOS-A) (N=122)	Patisiran (HELIOS-A) (N=42)
Western Europe		
Patients included in analysis, N1	42	20
<0 point increase from baseline, n(%)	27 (64.3)	11 (55.0)
≥0 point increase from baseline, n(%)	12 (28.6)	7 (35.0)
Missing, n(%)	3 (7.1)	2 (10.0)
<0 point increase from baseline, (95% CI)	64.3 (49.8, 78.8)	55.0 (33.2, 76.8)
Percentage difference (Vutrisiran – Patisiran), (95% CI)	9.286 (-16.894, 35.465)	
Odds ratio (Vutrisiran/Patisiran), (95% CI) [1]	1.473 (0.498, 4.353)	
Relative risk (Vutrisiran/Patisiran), (95% CI) [1]	1.169 (0.741, 1.844)	
P-value [2]	0.5025	

N1 = Patients with missing postbaseline values due to COVID-19 or after initiation of local standard treatment for hATTR amyloidosis were included in analysis.
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[2] p-value based on the Wald test testing whether the relative risk equals to 1.
[3] p-value from a logistic regression using the penalized likelihood estimation (the FIRTH option) and with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Table 3.6
Norfolk Quality of Life - Diabetic Neuropathy (QoL-DN) Total Score: Binary Subgroup Analysis
mITT Population

Month 18

Analysis Visit Statistics	Vutrisiran (HELIOS-A) (N=122)	Patisiran (HELIOS-A) (N=42)
Rest of World		
Patients included in analysis, N1	53	14
<0 point increase from baseline, n(%)	27 (50.9)	6 (42.9)
≥0 point increase from baseline, n(%)	23 (43.4)	7 (50.0)
Missing, n(%)	3 (5.7)	1 (7.1)
<0 point increase from baseline, (95% CI)	50.9 (37.5, 64.4)	42.9 (16.9, 68.8)
Percentage difference (Vutrisiran – Patisiran), (95% CI)	8.086 (-21.122, 37.294)	
Odds ratio (Vutrisiran/Patisiran), (95% CI) [1]	1.385 (0.422, 4.541)	
Relative risk (Vutrisiran/Patisiran), (95% CI) [1]	1.189 (0.614, 2.300)	
P-value [2]	0.6078	
p-value of Treatment*Region [3]	0.9503	

N1 = Patients with missing postbaseline values due to COVID-19 or after initiation of local standard treatment for hATTR amyloidosis were included in analysis.
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[2] p-value based on the Wald test testing whether the relative risk equals to 1.
[3] p-value from a logistic regression using the penalized likelihood estimation (the FIRTH option) and with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Table 3.6
Norfolk Quality of Life - Diabetic Neuropathy (QoL-DN) Total Score: Binary Subgroup Analysis
mITT Population

Month 9

Analysis Visit Statistics	Vutrisiran (HELIOS-A) (N=122)	Patisiran (HELIOS-A) (N=42)
Baseline NIS		
<50		
Patients included in analysis, N1	78	27
<0 point increase from baseline, n(%)	47 (60.3)	17 (63.0)
≥0 point increase from baseline, n(%)	29 (37.2)	10 (37.0)
Missing, n(%)	2 (2.6)	0
<0 point increase from baseline, (95% CI)	60.3 (49.4, 71.1)	63.0 (44.7, 81.2)
Percentage difference (Vutrisiran – Patisiran), (95% CI)	-2.707 (-23.913, 18.500)	
Odds ratio (Vutrisiran/Patisiran), (95% CI) [1]	0.892 (0.361, 2.201)	
Relative risk (Vutrisiran/Patisiran), (95% CI) [1]	0.957 (0.681, 1.346)	
P-value [2]	0.8005	

N1 = Patients with missing postbaseline values due to COVID-19 or after initiation of local standard treatment for hATTR amyloidosis were included in analysis.
[1] Based on unstratified analysis.
In estimation of the odds ratio and relative risk, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the percentage difference or p-value.
[2] p-value based on the Wald test testing whether the relative risk equals to 1.
[3] p-value from a logistic regression using the penalized likelihood estimation (the FIRTH option) and with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Table 3.6
Norfolk Quality of Life - Diabetic Neuropathy (QoL-DN) Total Score: Binary Subgroup Analysis
mITT Population

Month 9

Analysis Visit Statistics	Vutrisiran (HELIOS-A) (N=122)	Patisiran (HELIOS-A) (N=42)
≥50		
Patients included in analysis, N1	44	15
<0 point increase from baseline, n(%)	17 (38.6)	6 (40.0)
≥0 point increase from baseline, n(%)	22 (50.0)	7 (46.7)
Missing, n(%)	5 (11.4)	2 (13.3)
<0 point increase from baseline, (95% CI)	38.6 (24.2, 53.0)	40.0 (15.2, 64.8)
Percentage difference (Vutrisiran – Patisiran), (95% CI)	-1.364 (-30.028, 27.300)	
Odds ratio (Vutrisiran/Patisiran), (95% CI) [1]	0.944 (0.285, 3.130)	
Relative risk (Vutrisiran/Patisiran), (95% CI) [1]	0.966 (0.469, 1.990)	
P-value [2]	0.9251	
p-value of Treatment*Baseline NIS [3]	0.9710	

N1 = Patients with missing postbaseline values due to COVID-19 or after initiation of local standard treatment for hATTR amyloidosis were included in analysis.
[1] Based on unstratified analysis.
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[2] p-value based on the Wald test testing whether the relative risk equals to 1.
[3] p-value from a logistic regression using the penalized likelihood estimation (the FIRTH option) and with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Table 3.6
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mITT Population

Month 18

Analysis Visit Statistics	Vutrisiran (HELIOS-A) (N=122)	Patisiran (HELIOS-A) (N=42)
Baseline NIS		
<50		
Patients included in analysis, N1	78	27
<0 point increase from baseline, n(%)	50 (64.1)	14 (51.9)
≥0 point increase from baseline, n(%)	24 (30.8)	12 (44.4)
Missing, n(%)	4 (5.1)	1 (3.7)
<0 point increase from baseline, (95% CI)	64.1 (53.5, 74.7)	51.9 (33.0, 70.7)
Percentage difference (Vutrisiran – Patisiran), (95% CI)	12.251 (-9.395, 33.896)	
Odds ratio (Vutrisiran/Patisiran), (95% CI) [1]	1.658 (0.684, 4.019)	
Relative risk (Vutrisiran/Patisiran), (95% CI) [1]	1.236 (0.829, 1.844)	
P-value [2]	0.2982	

N1 = Patients with missing postbaseline values due to COVID-19 or after initiation of local standard treatment for hATTR amyloidosis were included in analysis.
[1] Based on unstratified analysis.
In estimation of the odds ratio and relative risk, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the percentage difference or p-value.
[2] p-value based on the Wald test testing whether the relative risk equals to 1.
[3] p-value from a logistic regression using the penalized likelihood estimation (the FIRTH option) and with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Table 3.6
Norfolk Quality of Life - Diabetic Neuropathy (QoL-DN) Total Score: Binary Subgroup Analysis
mITT Population

Month 18

Analysis Visit Statistics	Vutrisiran (HELIOS-A) (N=122)	Patisiran (HELIOS-A) (N=42)
≥50		
Patients included in analysis, N1	44	15
<0 point increase from baseline, n(%)	18 (40.9)	7 (46.7)
≥0 point increase from baseline, n(%)	21 (47.7)	5 (33.3)
Missing, n(%)	5 (11.4)	3 (20.0)
<0 point increase from baseline, (95% CI)	40.9 (26.4, 55.4)	46.7 (21.4, 71.9)
Percentage difference (Vutrisiran – Patisiran), (95% CI)	-5.758 (-34.886, 23.371)	
Odds ratio (Vutrisiran/Patisiran), (95% CI) [1]	0.791 (0.243, 2.572)	
Relative risk (Vutrisiran/Patisiran), (95% CI) [1]	0.877 (0.459, 1.674)	
P-value [2]	0.6900	
p-value of Treatment*Baseline NIS [3]	0.3286	

N1 = Patients with missing postbaseline values due to COVID-19 or after initiation of local standard treatment for hATTR amyloidosis were included in analysis.
[1] Based on unstratified analysis.
In estimation of the odds ratio and relative risk, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the percentage difference or p-value.
[2] p-value based on the Wald test testing whether the relative risk equals to 1.
[3] p-value from a logistic regression using the penalized likelihood estimation (the FIRTH option) and with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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mITT Population

Month 9

Analysis Visit Statistics	Vutrisiran (HELIOS-A) (N=122)	Patisiran (HELIOS-A) (N=42)
Previous Tetramer Stabilizer Use		
Yes		
Patients included in analysis, N1	75	33
<0 point increase from baseline, n(%)	37 (49.3)	18 (54.5)
≥0 point increase from baseline, n(%)	37 (49.3)	14 (42.4)
Missing, n(%)	1 (1.3)	1 (3.0)
<0 point increase from baseline, (95% CI)	49.3 (38.0, 60.6)	54.5 (37.6, 71.5)
Percentage difference (Vutrisiran – Patisiran), (95% CI)	-5.212 (-25.624, 15.200)	
Odds ratio (Vutrisiran/Patisiran), (95% CI) [1]	0.811 (0.357, 1.845)	
Relative risk (Vutrisiran/Patisiran), (95% CI) [1]	0.904 (0.614, 1.332)	
P-value [2]	0.6108	

N1 = Patients with missing postbaseline values due to COVID-19 or after initiation of local standard treatment for hATTR amyloidosis were included in analysis.
[1] Based on unstratified analysis.
In estimation of the odds ratio and relative risk, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the percentage difference or p-value.
[2] p-value based on the Wald test testing whether the relative risk equals to 1.
[3] p-value from a logistic regression using the penalized likelihood estimation (the FIRTH option) and with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Table 3.6
Norfolk Quality of Life - Diabetic Neuropathy (QoL-DN) Total Score: Binary Subgroup Analysis
mITT Population

Month 9

Analysis Visit Statistics	Vutrisiran (HELIOS-A) (N=122)	Patisiran (HELIOS-A) (N=42)
No		
Patients included in analysis, N1	47	9
<0 point increase from baseline, n(%)	27 (57.4)	5 (55.6)
≥0 point increase from baseline, n(%)	14 (29.8)	3 (33.3)
Missing, n(%)	6 (12.8)	1 (11.1)
<0 point increase from baseline, (95% CI)	57.4 (43.3, 71.6)	55.6 (23.1, 88.0)
Percentage difference (Vutrisiran – Patisiran), (95% CI)	1.891 (-33.516, 37.299)	
Odds ratio (Vutrisiran/Patisiran), (95% CI) [1]	1.080 (0.257, 4.542)	
Relative risk (Vutrisiran/Patisiran), (95% CI) [1]	1.034 (0.549, 1.949)	
P-value [2]	0.9176	
p-value of Treatment*Previous Tetramer Stabilizer Use [3]	0.7254	

N1 = Patients with missing postbaseline values due to COVID-19 or after initiation of local standard treatment for hATTR amyloidosis were included in analysis.
[1] Based on unstratified analysis.
In estimation of the odds ratio and relative risk, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the percentage difference or p-value.
[2] p-value based on the Wald test testing whether the relative risk equals to 1.
[3] p-value from a logistic regression using the penalized likelihood estimation (the FIRTH option) and with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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ALN-TTRSC02-002

Table 3.6
Norfolk Quality of Life - Diabetic Neuropathy (QoL-DN) Total Score: Binary Subgroup Analysis
mITT Population

Month 18

Analysis Visit Statistics	Vutrisiran (HELIOS-A) (N=122)	Patisiran (HELIOS-A) (N=42)
Previous Tetramer Stabilizer Use		
Yes		
Patients included in analysis, N1	75	33
<0 point increase from baseline, n(%)	40 (53.3)	17 (51.5)
≥0 point increase from baseline, n(%)	31 (41.3)	14 (42.4)
Missing, n(%)	4 (5.3)	2 (6.1)
<0 point increase from baseline, (95% CI)	53.3 (42.0, 64.6)	51.5 (34.5, 68.6)
Percentage difference (Vutrisiran − Patisiran), (95% CI)	1.818 (-18.633, 22.269)	
Odds ratio (Vutrisiran/Patisiran), (95% CI) [1]	1.076 (0.474, 2.441)	
Relative risk (Vutrisiran/Patisiran), (95% CI) [1]	1.035 (0.699, 1.534)	
P-value [2]	0.8626	

N1 = Patients with missing postbaseline values due to COVID-19 or after initiation of local standard treatment for hATTR amyloidosis were included in analysis.
[1] Based on unstratified analysis.
In estimation of the odds ratio and relative risk, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the percentage difference or p-value.
[2] p-value based on the Wald test testing whether the relative risk equals to 1.
[3] p-value from a logistic regression using the penalized likelihood estimation (the FIRTH option) and with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

Alnylam Pharmaceuticals Inc.
ALN-TTRSC02-002

Table 3.6
Norfolk Quality of Life - Diabetic Neuropathy (QoL-DN) Total Score: Binary Subgroup Analysis
mITT Population

Month 18

Analysis Visit Statistics	Vutrisiran (HELIOS-A) (N=122)	Patisiran (HELIOS-A) (N=42)
No		
Patients included in analysis, N1	47	9
<0 point increase from baseline, n(%)	28 (59.6)	4 (44.4)
≥0 point increase from baseline, n(%)	14 (29.8)	3 (33.3)
Missing, n(%)	5 (10.6)	2 (22.2)
<0 point increase from baseline, (95% CI)	59.6 (45.5, 73.6)	44.4 (12.0, 76.9)
Percentage difference (Vutrisiran – Patisiran), (95% CI)	15.130 (-20.236, 50.496)	
Odds ratio (Vutrisiran/Patisiran), (95% CI) [1]	1.842 (0.437, 7.760)	
Relative risk (Vutrisiran/Patisiran), (95% CI) [1]	1.340 (0.622, 2.888)	
P-value [2]	0.4543	
p-value of Treatment*Previous Tetramer Stabilizer Use [3]	0.5473	

N1 = Patients with missing postbaseline values due to COVID-19 or after initiation of local standard treatment for hATTR amyloidosis were included in analysis.
[1] Based on unstratified analysis.
In estimation of the odds ratio and relative risk, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the percentage difference or p-value.
[2] p-value based on the Wald test testing whether the relative risk equals to 1.
[3] p-value from a logistic regression using the penalized likelihood estimation (the FIRTH option) and with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Alnylam Pharmaceuticals Inc.
ALN-TTRSC02-002

Table 3.6
Norfolk Quality of Life - Diabetic Neuropathy (QoL-DN) Total Score: Binary Subgroup Analysis
mITT Population

Month 9

Analysis Visit Statistics	Vutrisiran (HELIOS-A) (N=122)	Patisiran (HELIOS-A) (N=42)
Genotype		
V30M		
Patients included in analysis, N1	54	20
<0 point increase from baseline, n(%)	30 (55.6)	14 (70.0)
≥0 point increase from baseline, n(%)	21 (38.9)	6 (30.0)
Missing, n(%)	3 (5.6)	0
<0 point increase from baseline, (95% CI)	55.6 (42.3, 68.8)	70.0 (49.9, 90.1)
Percentage difference (Vutrisiran − Patisiran), (95% CI)	-14.444 (-38.507, 9.618)	
Odds ratio (Vutrisiran/Patisiran), (95% CI) [1]	0.536 (0.179, 1.604)	
Relative risk (Vutrisiran/Patisiran), (95% CI) [1]	0.794 (0.546, 1.153)	
P-value [2]	0.2248	

N1 = Patients with missing postbaseline values due to COVID-19 or after initiation of local standard treatment for hATTR amyloidosis were included in analysis.
[1] Based on unstratified analysis.
In estimation of the odds ratio and relative risk, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the percentage difference or p-value.
[2] p-value based on the Wald test testing whether the relative risk equals to 1.
[3] p-value from a logistic regression using the penalized likelihood estimation (the FIRTH option) and with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Alnylam Pharmaceuticals Inc.
ALN-TTRSC02-002

Table 3.6
Norfolk Quality of Life - Diabetic Neuropathy (QoL-DN) Total Score: Binary Subgroup Analysis
mITT Population

Month 9

Analysis Visit Statistics	Vutrisiran (HELIOS-A) (N=122)	Patisiran (HELIOS-A) (N=42)
non-V30M		
Patients included in analysis, N1	68	22
<0 point increase from baseline, n(%)	34 (50.0)	9 (40.9)
≥0 point increase from baseline, n(%)	30 (44.1)	11 (50.0)
Missing, n(%)	4 (5.9)	2 (9.1)
<0 point increase from baseline, (95% CI)	50.0 (38.1, 61.9)	40.9 (20.4, 61.5)
Percentage difference (Vutrisiran – Patisiran), (95% CI)	9.091 (-14.644, 32.825)	
Odds ratio (Vutrisiran/Patisiran), (95% CI) [1]	1.444 (0.545, 3.825)	
Relative risk (Vutrisiran/Patisiran), (95% CI) [1]	1.222 (0.701, 2.130)	
P-value [2]	0.4790	
p-value of Treatment*Genotype [3]	0.2097	

N1 = Patients with missing postbaseline values due to COVID-19 or after initiation of local standard treatment for hATTR amyloidosis were included in analysis.
[1] Based on unstratified analysis.
In estimation of the odds ratio and relative risk, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the percentage difference or p-value.
[2] p-value based on the Wald test testing whether the relative risk equals to 1.
[3] p-value from a logistic regression using the penalized likelihood estimation (the FIRTH option) and with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Table 3.6
Norfolk Quality of Life - Diabetic Neuropathy (QoL-DN) Total Score: Binary Subgroup Analysis
mITT Population

Month 18

Analysis Visit Statistics	Vutrisiran (HELIOS-A) (N=122)	Patisiran (HELIOS-A) (N=42)
Genotype		
V30M		
Patients included in analysis, N1	54	20
<0 point increase from baseline, n(%)	31 (57.4)	14 (70.0)
≥0 point increase from baseline, n(%)	20 (37.0)	6 (30.0)
Missing, n(%)	3 (5.6)	0
<0 point increase from baseline, (95% CI)	57.4 (44.2, 70.6)	70.0 (49.9, 90.1)
Percentage difference (Vutrisiran – Patisiran), (95% CI)	-12.593 (-36.620, 11.434)	
Odds ratio (Vutrisiran/Patisiran), (95% CI) [1]	0.578 (0.193, 1.732)	
Relative risk (Vutrisiran/Patisiran), (95% CI) [1]	0.820 (0.568, 1.184)	
P-value [2]	0.2903	

N1 = Patients with missing postbaseline values due to COVID-19 or after initiation of local standard treatment for hATTR amyloidosis were included in analysis.
[1] Based on unstratified analysis.
In estimation of the odds ratio and relative risk, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the percentage difference or p-value.
[2] p-value based on the Wald test testing whether the relative risk equals to 1.
[3] p-value from a logistic regression using the penalized likelihood estimation (the FIRTH option) and with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Table 3.6
Norfolk Quality of Life - Diabetic Neuropathy (QoL-DN) Total Score: Binary Subgroup Analysis
mITT Population

Month 18

Analysis Visit Statistics	Vutrisiran (HELIOS-A) (N=122)	Patisiran (HELIOS-A) (N=42)
non-V30M		
Patients included in analysis, N1	68	22
<0 point increase from baseline, n(%)	37 (54.4)	7 (31.8)
≥0 point increase from baseline, n(%)	25 (36.8)	11 (50.0)
Missing, n(%)	6 (8.8)	4 (18.2)
<0 point increase from baseline, (95% CI)	54.4 (42.6, 66.2)	31.8 (12.4, 51.3)
Percentage difference (Vutrisiran – Patisiran), (95% CI)	22.594 (-0.187, 45.374)	
Odds ratio (Vutrisiran/Patisiran), (95% CI) [1]	2.558 (0.926, 7.066)	
Relative risk (Vutrisiran/Patisiran), (95% CI) [1]	1.710 (0.893, 3.273)	
P-value [2]	0.1053	
p-value of Treatment*Genotype [3]	0.0632	

N1 = Patients with missing postbaseline values due to COVID-19 or after initiation of local standard treatment for hATTR amyloidosis were included in analysis.
[1] Based on unstratified analysis.
In estimation of the odds ratio and relative risk, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the percentage difference or p-value.
[2] p-value based on the Wald test testing whether the relative risk equals to 1.
[3] p-value from a logistic regression using the penalized likelihood estimation (the FIRTH option) and with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Table 3.6
Norfolk Quality of Life - Diabetic Neuropathy (QoL-DN) Total Score: Binary Subgroup Analysis
mITT Population

Month 9

Analysis Visit Statistics	Vutrisiran (HELIOS-A) (N=122)	Patisiran (HELIOS-A) (N=42)
FAP Stage		
I		
Patients included in analysis, N1	84	31
<0 point increase from baseline, n(%)	50 (59.5)	18 (58.1)
≥0 point increase from baseline, n(%)	31 (36.9)	12 (38.7)
Missing, n(%)	3 (3.6)	1 (3.2)
<0 point increase from baseline, (95% CI)	59.5 (49.0, 70.0)	58.1 (40.7, 75.4)
Percentage difference (Vutrisiran − Patisiran), (95% CI)	1.459 (-18.836, 21.755)	
Odds ratio (Vutrisiran/Patisiran), (95% CI) [1]	1.062 (0.460, 2.450)	
Relative risk (Vutrisiran/Patisiran), (95% CI) [1]	1.025 (0.724, 1.451)	
P-value [2]	0.8886	

N1 = Patients with missing postbaseline values due to COVID-19 or after initiation of local standard treatment for hATTR amyloidosis were included in analysis.
[1] Based on unstratified analysis.
In estimation of the odds ratio and relative risk, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the percentage difference or p-value.
[2] p-value based on the Wald test testing whether the relative risk equals to 1.
[3] p-value from a logistic regression using the penalized likelihood estimation (the FIRTH option) and with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Table 3.6
Norfolk Quality of Life - Diabetic Neuropathy (QoL-DN) Total Score: Binary Subgroup Analysis
mITT Population

Month 9

Analysis Visit Statistics	Vutrisiran (HELIOS-A) (N=122)	Patisiran (HELIOS-A) (N=42)
II&III		
Patients included in analysis, N1	38	11
<0 point increase from baseline, n(%)	14 (36.8)	5 (45.5)
≥0 point increase from baseline, n(%)	20 (52.6)	5 (45.5)
Missing, n(%)	4 (10.5)	1 (9.1)
<0 point increase from baseline, (95% CI)	36.8 (21.5, 52.2)	45.5 (16.0, 74.9)
Percentage difference (Vutrisiran – Patisiran), (95% CI)	-8.612 (-41.795, 24.570)	
Odds ratio (Vutrisiran/Patisiran), (95% CI) [1]	0.700 (0.180, 2.721)	
Relative risk (Vutrisiran/Patisiran), (95% CI) [1]	0.811 (0.375, 1.750)	
P-value [2]	0.5927	
p-value of Treatment*FAP Stage [3]	0.6026	

N1 = Patients with missing postbaseline values due to COVID-19 or after initiation of local standard treatment for hATTR amyloidosis were included in analysis.
[1] Based on unstratified analysis.
In estimation of the odds ratio and relative risk, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the percentage difference or p-value.
[2] p-value based on the Wald test testing whether the relative risk equals to 1.
[3] p-value from a logistic regression using the penalized likelihood estimation (the FIRTH option) and with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Table 3.6
Norfolk Quality of Life - Diabetic Neuropathy (QoL-DN) Total Score: Binary Subgroup Analysis
mITT Population

Month 18

Analysis Visit Statistics	Vutrisiran (HELIOS-A) (N=122)	Patisiran (HELIOS-A) (N=42)
FAP Stage		
I		
Patients included in analysis, N1	84	31
<0 point increase from baseline, n(%)	50 (59.5)	18 (58.1)
≥0 point increase from baseline, n(%)	30 (35.7)	12 (38.7)
Missing, n(%)	4 (4.8)	1 (3.2)
<0 point increase from baseline, (95% CI)	59.5 (49.0, 70.0)	58.1 (40.7, 75.4)
Percentage difference (Vutrisiran − Patisiran), (95% CI)	1.459 (-18.836, 21.755)	
Odds ratio (Vutrisiran/Patisiran), (95% CI) [1]	1.062 (0.460, 2.450)	
Relative risk (Vutrisiran/Patisiran), (95% CI) [1]	1.025 (0.724, 1.451)	
P-value [2]	0.8886	

N1 = Patients with missing postbaseline values due to COVID-19 or after initiation of local standard treatment for hATTR amyloidosis were included in analysis.
[1] Based on unstratified analysis.
In estimation of the odds ratio and relative risk, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the percentage difference or p-value.
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[3] p-value from a logistic regression using the penalized likelihood estimation (the FIRTH option) and with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Table 3.6
Norfolk Quality of Life - Diabetic Neuropathy (QoL-DN) Total Score: Binary Subgroup Analysis
mITT Population

Month 18

Analysis Visit Statistics	Vutrisiran (HELIOS-A) (N=122)	Patisiran (HELIOS-A) (N=42)
II&III		
Patients included in analysis, N1	38	11
<0 point increase from baseline, n(%)	18 (47.4)	3 (27.3)
≥0 point increase from baseline, n(%)	15 (39.5)	5 (45.5)
Missing, n(%)	5 (13.2)	3 (27.3)
<0 point increase from baseline, (95% CI)	47.4 (31.5, 63.2)	27.3 (1.0, 53.6)
Percentage difference (Vutrisiran – Patisiran), (95% CI)	20.096 (-10.640, 50.832)	
Odds ratio (Vutrisiran/Patisiran), (95% CI) [1]	2.400 (0.551, 10.457)	
Relative risk (Vutrisiran/Patisiran), (95% CI) [1]	1.737 (0.625, 4.824)	
P-value [2]	0.2895	
p-value of Treatment*FAP Stage [3]	0.3991	

N1 = Patients with missing postbaseline values due to COVID-19 or after initiation of local standard treatment for hATTR amyloidosis were included in analysis.
[1] Based on unstratified analysis.
In estimation of the odds ratio and relative risk, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the percentage difference or p-value.
[2] p-value based on the Wald test testing whether the relative risk equals to 1.
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Table 3.6
Norfolk Quality of Life - Diabetic Neuropathy (QoL-DN) Total Score: Binary Subgroup Analysis
mITT Population

Month 9

Analysis Visit Statistics	Vutrisiran (HELIOS-A) (N=122)	Patisiran (HELIOS-A) (N=42)
Cardiac Subpopulation		
Yes		
Patients included in analysis, N1	40	14
<0 point increase from baseline, n(%)	22 (55.0)	7 (50.0)
≥0 point increase from baseline, n(%)	16 (40.0)	7 (50.0)
Missing, n(%)	2 (5.0)	0
<0 point increase from baseline, (95% CI)	55.0 (39.6, 70.4)	50.0 (23.8, 76.2)
Percentage difference (Vutrisiran – Patisiran), (95% CI)	5.000 (-25.392, 35.392)	
Odds ratio (Vutrisiran/Patisiran), (95% CI) [1]	1.222 (0.361, 4.135)	
Relative risk (Vutrisiran/Patisiran), (95% CI) [1]	1.100 (0.607, 1.993)	
P-value [2]	0.7532	

N1 = Patients with missing postbaseline values due to COVID-19 or after initiation of local standard treatment for hATTR amyloidosis were included in analysis.
[1] Based on unstratified analysis.
In estimation of the odds ratio and relative risk, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the percentage difference or p-value.
[2] p-value based on the Wald test testing whether the relative risk equals to 1.
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Table 3.6
Norfolk Quality of Life - Diabetic Neuropathy (QoL-DN) Total Score: Binary Subgroup Analysis
mITT Population

Month 9

Analysis Visit Statistics	Vutrisiran (HELIOS-A) (N=122)	Patisiran (HELIOS-A) (N=42)
No		
Patients included in analysis, N1	82	28
<0 point increase from baseline, n(%)	42 (51.2)	16 (57.1)
≥0 point increase from baseline, n(%)	35 (42.7)	10 (35.7)
Missing, n(%)	5 (6.1)	2 (7.1)
<0 point increase from baseline, (95% CI)	51.2 (40.4, 62.0)	57.1 (38.8, 75.5)
Percentage difference (Vutrisiran – Patisiran), (95% CI)	-5.923 (-27.208, 15.361)	
Odds ratio (Vutrisiran/Patisiran), (95% CI) [1]	0.788 (0.332, 1.870)	
Relative risk (Vutrisiran/Patisiran), (95% CI) [1]	0.896 (0.610, 1.316)	
P-value [2]	0.5765	
p-value of Treatment*Cardiac Subpopulation [3]	0.5770	

N1 = Patients with missing postbaseline values due to COVID-19 or after initiation of local standard treatment for hATTR amyloidosis were included in analysis.
[1] Based on unstratified analysis.
In estimation of the odds ratio and relative risk, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the percentage difference or p-value.
[2] p-value based on the Wald test testing whether the relative risk equals to 1.
[3] p-value from a logistic regression using the penalized likelihood estimation (the FIRTH option) and with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Table 3.6
Norfolk Quality of Life - Diabetic Neuropathy (QoL-DN) Total Score: Binary Subgroup Analysis
mITT Population

Month 18

Analysis Visit Statistics	Vutrisiran (HELIOS-A) (N=122)	Patisiran (HELIOS-A) (N=42)
Cardiac Subpopulation		
Yes		
Patients included in analysis, N1	40	14
<0 point increase from baseline, n(%)	23 (57.5)	6 (42.9)
≥0 point increase from baseline, n(%)	14 (35.0)	7 (50.0)
Missing, n(%)	3 (7.5)	1 (7.1)
<0 point increase from baseline, (95% CI)	57.5 (42.2, 72.8)	42.9 (16.9, 68.8)
Percentage difference (Vutrisiran − Patisiran), (95% CI)	14.643 (-15.468, 44.754)	
Odds ratio (Vutrisiran/Patisiran), (95% CI) [1]	1.804 (0.527, 6.173)	
Relative risk (Vutrisiran/Patisiran), (95% CI) [1]	1.342 (0.693, 2.598)	
P-value [2]	0.3834	

N1 = Patients with missing postbaseline values due to COVID-19 or after initiation of local standard treatment for hATTR amyloidosis were included in analysis.
[1] Based on unstratified analysis.
In estimation of the odds ratio and relative risk, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the percentage difference or p-value.
[2] p-value based on the Wald test testing whether the relative risk equals to 1.
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Table 3.6
Norfolk Quality of Life - Diabetic Neuropathy (QoL-DN) Total Score: Binary Subgroup Analysis
mITT Population

Month 18

Analysis Visit Statistics	Vutrisiran (HELIOS-A) (N=122)	Patisiran (HELIOS-A) (N=42)
No		
Patients included in analysis, N1	82	28
<0 point increase from baseline, n(%)	45 (54.9)	15 (53.6)
≥0 point increase from baseline, n(%)	31 (37.8)	10 (35.7)
Missing, n(%)	6 (7.3)	3 (10.7)
<0 point increase from baseline, (95% CI)	54.9 (44.1, 65.6)	53.6 (35.1, 72.0)
Percentage difference (Vutrisiran – Patisiran), (95% CI)	1.307 (-20.077, 22.690)	
Odds ratio (Vutrisiran/Patisiran), (95% CI) [1]	1.054 (0.446, 2.493)	
Relative risk (Vutrisiran/Patisiran), (95% CI) [1]	1.024 (0.689, 1.523)	
P-value [2]	0.9052	
p-value of Treatment*Cardiac Subpopulation [3]	0.5069	

N1 = Patients with missing postbaseline values due to COVID-19 or after initiation of local standard treatment for hATTR amyloidosis were included in analysis.
[1] Based on unstratified analysis.
In estimation of the odds ratio and relative risk, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the percentage difference or p-value.
[2] p-value based on the Wald test testing whether the relative risk equals to 1.
[3] p-value from a logistic regression using the penalized likelihood estimation (the FIRTH option) and with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Table 3.6
Norfolk Quality of Life - Diabetic Neuropathy (QoL-DN) Total Score: Binary Subgroup Analysis
mITT Population

Month 9

Analysis Visit Statistics	Vutrisiran (HELIOS-A) (N=122)	Patisiran (HELIOS-A) (N=42)
Weight (kg)		
<65 kg		
Patients included in analysis, N1	46	15
<0 point increase from baseline, n(%)	26 (56.5)	10 (66.7)
≥0 point increase from baseline, n(%)	18 (39.1)	5 (33.3)
Missing, n(%)	2 (4.3)	0
<0 point increase from baseline, (95% CI)	56.5 (42.2, 70.8)	66.7 (42.8, 90.5)
Percentage difference (Vutrisiran – Patisiran), (95% CI)	-10.145 (-37.972, 17.682)	
Odds ratio (Vutrisiran/Patisiran), (95% CI) [1]	0.650 (0.192, 2.205)	
Relative risk (Vutrisiran/Patisiran), (95% CI) [1]	0.848 (0.547, 1.314)	
P-value [2]	0.4606	

N1 = Patients with missing postbaseline values due to COVID-19 or after initiation of local standard treatment for hATTR amyloidosis were included in analysis.
[1] Based on unstratified analysis.
In estimation of the odds ratio and relative risk, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the percentage difference or p-value.
[2] p-value based on the Wald test testing whether the relative risk equals to 1.
[3] p-value from a logistic regression using the penalized likelihood estimation (the FIRTH option) and with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Alnylam Pharmaceuticals Inc.
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Table 3.6
Norfolk Quality of Life - Diabetic Neuropathy (QoL-DN) Total Score: Binary Subgroup Analysis
mITT Population

Month 9

Analysis Visit Statistics	Vutrisiran (HELIOS-A) (N=122)	Patisiran (HELIOS-A) (N=42)
≥65 kg		
Patients included in analysis, N1	76	27
<0 point increase from baseline, n(%)	38 (50.0)	13 (48.1)
≥0 point increase from baseline, n(%)	33 (43.4)	12 (44.4)
Missing, n(%)	5 (6.6)	2 (7.4)
<0 point increase from baseline, (95% CI)	50.0 (38.8, 61.2)	48.1 (29.3, 67.0)
Percentage difference (Vutrisiran – Patisiran), (95% CI)	1.852 (-20.093, 23.796)	
Odds ratio (Vutrisiran/Patisiran), (95% CI) [1]	1.077 (0.447, 2.593)	
Relative risk (Vutrisiran/Patisiran), (95% CI) [1]	1.038 (0.661, 1.631)	
P-value [2]	0.8698	
p-value of Treatment*Weight (kg) [3]	0.5463	

N1 = Patients with missing postbaseline values due to COVID-19 or after initiation of local standard treatment for hATTR amyloidosis were included in analysis.
[1] Based on unstratified analysis.
In estimation of the odds ratio and relative risk, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the percentage difference or p-value.
[2] p-value based on the Wald test testing whether the relative risk equals to 1.
[3] p-value from a logistic regression using the penalized likelihood estimation (the FIRTH option) and with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Alnylam Pharmaceuticals Inc.
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Table 3.6
Norfolk Quality of Life - Diabetic Neuropathy (QoL-DN) Total Score: Binary Subgroup Analysis
mITT Population

Month 18

Analysis Visit Statistics	Vutrisiran (HELIOS-A) (N=122)	Patisiran (HELIOS-A) (N=42)
Weight (kg)		
<65 kg		
Patients included in analysis, N1	46	15
<0 point increase from baseline, n(%)	20 (43.5)	8 (53.3)
≥0 point increase from baseline, n(%)	22 (47.8)	7 (46.7)
Missing, n(%)	4 (8.7)	0
<0 point increase from baseline, (95% CI)	43.5 (29.2, 57.8)	53.3 (28.1, 78.6)
Percentage difference (Vutrisiran – Patisiran), (95% CI)	-9.855 (-38.883, 19.173)	
Odds ratio (Vutrisiran/Patisiran), (95% CI) [1]	0.673 (0.209, 2.169)	
Relative risk (Vutrisiran/Patisiran), (95% CI) [1]	0.815 (0.458, 1.451)	
P-value [2]	0.4875	

N1 = Patients with missing postbaseline values due to COVID-19 or after initiation of local standard treatment for hATTR amyloidosis were included in analysis.
[1] Based on unstratified analysis.
In estimation of the odds ratio and relative risk, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the percentage difference or p-value.
[2] p-value based on the Wald test testing whether the relative risk equals to 1.
[3] p-value from a logistic regression using the penalized likelihood estimation (the FIRTH option) and with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Alnylam Pharmaceuticals Inc.
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Table 3.6
Norfolk Quality of Life - Diabetic Neuropathy (QoL-DN) Total Score: Binary Subgroup Analysis
mITT Population

Month 18

Analysis Visit Statistics	Vutrisiran (HELIOS-A) (N=122)	Patisiran (HELIOS-A) (N=42)
≥65 kg		
Patients included in analysis, N1	76	27
<0 point increase from baseline, n(%)	48 (63.2)	13 (48.1)
≥0 point increase from baseline, n(%)	23 (30.3)	10 (37.0)
Missing, n(%)	5 (6.6)	4 (14.8)
<0 point increase from baseline, (95% CI)	63.2 (52.3, 74.0)	48.1 (29.3, 67.0)
Percentage difference (Vutrisiran – Patisiran), (95% CI)	15.010 (-6.735, 36.754)	
Odds ratio (Vutrisiran/Patisiran), (95% CI) [1]	1.846 (0.760, 4.483)	
Relative risk (Vutrisiran/Patisiran), (95% CI) [1]	1.312 (0.855, 2.011)	
P-value [2]	0.2134	
p-value of Treatment*Weight (kg) [3]	0.1884	

N1 = Patients with missing postbaseline values due to COVID-19 or after initiation of local standard treatment for hATTR amyloidosis were included in analysis.
[1] Based on unstratified analysis.
In estimation of the odds ratio and relative risk, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the percentage difference or p-value.
[2] p-value based on the Wald test testing whether the relative risk equals to 1.
[3] p-value from a logistic regression using the penalized likelihood estimation (the FIRTH option) and with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Norfolk-QoL-DN – Domäne Physische Funktionen/Große Nervenfasern

Alnylam Pharmaceuticals Inc.
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Table 3.5
Norfolk Quality of Life - Diabetic Neuropathy (QoL-DN) Domain Scores: Change from Baseline to Month 18, MMRM Model
Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A) Subgroup Analysis
mITT Population

Norfolk QoL-DN Domain: Physical Functioning/Large Fiber

Subgroup Visit	LS Mean (95% CI) Vutrisiran (HELIOS-A) (N=122)	LS Mean (95% CI) Patisiran (HELIOS-A) (N=42)	LS Mean Difference (Vutrisiran-Patisiran) (95% CI), p-value	Standardized Effect Size (95% CI)
Age (years)				
<65	74	30		
Month 9	-2.58 (-4.83, -0.32)	-0.17 (-3.71, 3.38)	-2.41 (-6.60, 1.78), 0.2582	-0.24 (-0.67, 0.18)
Month 18	-1.94 (-4.31, 0.43)	-0.59 (-4.38, 3.19)	-1.34 (-5.80, 3.12), 0.5524	-0.12 (-0.55, 0.31)
≥65	43	10		
Month 9	-3.36 (-6.29, -0.44)	1.05 (-4.98, 7.07)	-4.41 (-11.10, 2.28), 0.1947	-0.44 (-1.13, 0.24)
Month 18	-2.73 (-5.75, 0.30)	0.62 (-5.56, 6.81)	-3.35 (-10.23, 3.53), 0.3383	-0.33 (-1.05, 0.38)
p-value of Treatment*Age	0.6117			

Norfolk QoL-DN score = composite of 35 quality of life questions; lower scores indicate higher quality of life (range = -4 to 136). Nonmissing scores for items 27-33 imputed for patients who reported an impact due to COVID-19 pandemic. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.
LS estimates and p-value derived from mixed-effects model for repeated measures (MMRM), controlling for categorical factors (treatment, visit), the subgroup variable, continuous covariate (baseline value), and interaction (treatment by visit, treatment by subgroup).
Standardized effect size (d) = LS mean difference/estimated pooled standard deviation with the small sample bias correction.

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Table 3.5
Norfolk Quality of Life - Diabetic Neuropathy (QoL-DN) Domain Scores: Change from Baseline to Month 18, MMRM Model
Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A) Subgroup Analysis
mITT Population

Norfolk QoL-DN Domain: Physical Functioning/Large Fiber

Subgroup Visit	LS Mean (95% CI) Vutrisiran (HELIOS-A) (N=122)	LS Mean (95% CI) Patisiran (HELIOS-A) (N=42)	LS Mean Difference (Vutrisiran-Patisiran) (95% CI), p-value	Standardized Effect Size (95% CI)
Sex				
Male	76	25		
Month 9	-2.67 (-4.90, -0.45)	-0.21 (-4.07, 3.66)	-2.46 (-6.92, 2.00), 0.2769	-0.24 (-0.69, 0.21)
Month 18	-2.03 (-4.37, 0.31)	-0.64 (-4.73, 3.45)	-1.39 (-6.10, 3.32), 0.5614	-0.12 (-0.59, 0.34)
Female	41	15		
Month 9	-3.22 (-6.22, -0.23)	0.71 (-4.22, 5.65)	-3.94 (-9.71, 1.84), 0.1800	-0.44 (-1.03, 0.15)
Month 18	-2.58 (-5.65, 0.49)	0.28 (-4.80, 5.36)	-2.86 (-8.80, 3.08), 0.3427	-0.30 (-0.89, 0.29)
p-value of Treatment*Sex	0.6845			

Norfolk QoL-DN score = composite of 35 quality of life questions; lower scores indicate higher quality of life (range = -4 to 136). Nonmissing scores for items 27-33 imputed for patients who reported an impact due to COVID-19 pandemic. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.
LS estimates and p-value derived from mixed-effects model for repeated measures (MMRM), controlling for categorical factors (treatment, visit), the subgroup variable, continuous covariate (baseline value), and interaction (treatment by visit, treatment by subgroup).
Standardized effect size (d) = LS mean difference/estimated pooled standard deviation with the small sample bias correction.

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Table 3.5
Norfolk Quality of Life - Diabetic Neuropathy (QoL-DN) Domain Scores: Change from Baseline to Month 18, MMRM Model
Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A) Subgroup Analysis
mITT Population

Norfolk QoL-DN Domain: Physical Functioning/Large Fiber

Subgroup Visit	LS Mean (95% CI) Vutrisiran (HELIOS-A) (N=122)	LS Mean (95% CI) Patisiran (HELIOS-A) (N=42)	LS Mean Difference (Vutrisiran-Patisiran) (95% CI), p-value	Standardized Effect Size (95% CI)
Race				
White	82	28		
Month 9	-2.00 (-4.13, 0.12)	0.28 (-3.35, 3.91)	-2.28 (-6.49, 1.92), 0.2853	-0.26 (-0.69, 0.16)
Month 18	-1.36 (-3.63, 0.91)	-0.15 (-4.04, 3.74)	-1.21 (-5.72, 3.29), 0.5960	-0.12 (-0.55, 0.32)
All Other Races	35	12		
Month 9	-4.89 (-8.10, -1.69)	-0.19 (-5.68, 5.30)	-4.70 (-11.06, 1.66), 0.1461	-0.39 (-1.04, 0.26)
Month 18	-4.25 (-7.56, -0.95)	-0.62 (-6.30, 5.06)	-3.63 (-10.20, 2.94), 0.2772	-0.31 (-0.99, 0.36)
p-value of Treatment*Race	0.5267			

Norfolk QoL-DN score = composite of 35 quality of life questions; lower scores indicate higher quality of life (range = -4 to 136). Nonmissing scores for items 27-33 imputed for patients who reported an impact due to COVID-19 pandemic. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.
LS estimates and p-value derived from mixed-effects model for repeated measures (MMRM), controlling for categorical factors (treatment, visit), the subgroup variable, continuous covariate (baseline value), and interaction (treatment by visit, treatment by subgroup).
Standardized effect size (d) = LS mean difference/estimated pooled standard deviation with the small sample bias correction.

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Table 3.5
Norfolk Quality of Life - Diabetic Neuropathy (QoL-DN) Domain Scores: Change from Baseline to Month 18, MMRM Model
Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A) Subgroup Analysis
mITT Population

Norfolk QoL-DN Domain: Physical Functioning/Large Fiber

Subgroup Visit	LS Mean (95% CI) Vutrisiran (HELIOS-A) (N=122)	LS Mean (95% CI) Patisiran (HELIOS-A) (N=42)	LS Mean Difference (Vutrisiran-Patisiran) (95% CI), p-value	Standardized Effect Size (95% CI)
Region				
North America	26	8		
Month 9	-6.03 (-9.73, -2.33)	-1.76 (-8.36, 4.83)	-4.26 (-11.83, 3.30), 0.2672	-0.43 (-1.22, 0.36)
Month 18	-5.38 (-9.14, -1.62)	-2.18 (-8.92, 4.56)	-3.20 (-10.92, 4.51), 0.4140	-0.24 (-1.06, 0.58)
Western Europe	39	18		
Month 9	-1.77 (-4.77, 1.23)	-2.30 (-6.73, 2.14)	0.53 (-4.83, 5.88), 0.8467	0.06 (-0.49, 0.61)
Month 18	-1.12 (-4.20, 1.95)	-2.71 (-7.30, 1.88)	1.59 (-3.94, 7.12), 0.5714	0.19 (-0.36, 0.74)
Rest of World	52	14		
Month 9	-2.14 (-4.75, 0.47)	4.35 (-0.67, 9.37)	-6.50 (-12.16, -0.84), 0.0247	-0.64 (-1.23, -0.05)
Month 18	-1.50 (-4.21, 1.21)	3.94 (-1.25, 9.13)	-5.44 (-11.29, 0.42), 0.0686	-0.50 (-1.11, 0.11)
p-value of Treatment*Region	0.1852			

Norfolk QoL-DN score = composite of 35 quality of life questions; lower scores indicate higher quality of life (range = -4 to 136). Nonmissing scores for items 27-33 imputed for patients who reported an impact due to COVID-19 pandemic. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.
LS estimates and p-value derived from mixed-effects model for repeated measures (MMRM), controlling for categorical factors (treatment, visit), the subgroup variable, continuous covariate (baseline value), and interaction (treatment by visit, treatment by subgroup).
Standardized effect size (d) = LS mean difference/estimated pooled standard deviation with the small sample bias correction.

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Table 3.5
Norfolk Quality of Life - Diabetic Neuropathy (QoL-DN) Domain Scores: Change from Baseline to Month 18, MMRM Model
Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A) Subgroup Analysis
mITT Population

Norfolk QoL-DN Domain: Physical Functioning/Large Fiber

Subgroup Visit	LS Mean (95% CI) Vutrisiran (HELIOS-A) (N=122)	LS Mean (95% CI) Patisiran (HELIOS-A) (N=42)	LS Mean Difference (Vutrisiran-Patisiran) (95% CI), p-value	Standardized Effect Size (95% CI)
Baseline NIS				
<50	76	27		
Month 9	-6.82 (-8.85, -4.80)	-2.42 (-5.78, 0.93)	-4.40 (-8.25, -0.55), 0.0254	-0.50 (-0.94, -0.06)
Month 18	-6.22 (-8.37, -4.06)	-2.88 (-6.46, 0.71)	-3.34 (-7.46, 0.77), 0.1104	-0.33 (-0.78, 0.11)
≥50	41	13		
Month 9	4.37 (1.60, 7.13)	5.20 (0.41, 9.98)	-0.83 (-6.22, 4.55), 0.7604	-0.09 (-0.71, 0.53)
Month 18	4.97 (2.13, 7.81)	4.75 (-0.21, 9.70)	0.22 (-5.36, 5.81), 0.9368	0.03 (-0.61, 0.66)
p-value of Treatment*Baseline NIS	0.2769			

Norfolk QoL-DN score = composite of 35 quality of life questions; lower scores indicate higher quality of life (range = -4 to 136). Nonmissing scores for items 27-33 imputed for patients who reported an impact due to COVID-19 pandemic. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.
LS estimates and p-value derived from mixed-effects model for repeated measures (MMRM), controlling for categorical factors (treatment, visit), the subgroup variable, continuous covariate (baseline value), and interaction (treatment by visit, treatment by subgroup).
Standardized effect size (d) = LS mean difference/estimated pooled standard deviation with the small sample bias correction.

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Table 3.5
Norfolk Quality of Life - Diabetic Neuropathy (QoL-DN) Domain Scores: Change from Baseline to Month 18, MMRM Model
Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A) Subgroup Analysis
mITT Population

Norfolk QoL-DN Domain: Physical Functioning/Large Fiber

Subgroup Visit	LS Mean (95% CI) Vutrisiran (HELIOS-A) (N=122)	LS Mean (95% CI) Patisiran (HELIOS-A) (N=42)	LS Mean Difference (Vutrisiran-Patisiran) (95% CI), p-value	Standardized Effect Size (95% CI)
Previous Tetramer Stabilizer Use				
Yes	74	32		
Month 9	-1.59 (-3.82, 0.64)	-0.02 (-3.42, 3.38)	-1.57 (-5.64, 2.50), 0.4467	-0.17 (-0.59, 0.24)
Month 18	-0.94 (-3.29, 1.42)	-0.44 (-4.08, 3.19)	-0.49 (-4.82, 3.84), 0.8236	-0.05 (-0.47, 0.37)
No	43	8		
Month 9	-5.08 (-7.98, -2.17)	0.80 (-5.86, 7.46)	-5.87 (-13.15, 1.40), 0.1128	-0.52 (-1.27, 0.23)
Month 18	-4.42 (-7.40, -1.44)	0.37 (-6.44, 7.18)	-4.79 (-12.24, 2.65), 0.2056	-0.38 (-1.17, 0.41)
p-value of Treatment*Previous Tetramer Stabilizer Use	0.3036			

Norfolk QoL-DN score = composite of 35 quality of life questions; lower scores indicate higher quality of life (range = -4 to 136). Nonmissing scores for items 27-33 imputed for patients who reported an impact due to COVID-19 pandemic. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.
LS estimates and p-value derived from mixed-effects model for repeated measures (MMRM), controlling for categorical factors (treatment, visit), the subgroup variable, continuous covariate (baseline value), and interaction (treatment by visit, treatment by subgroup).
Standardized effect size (d) = LS mean difference/estimated pooled standard deviation with the small sample bias correction.

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Table 3.5
Norfolk Quality of Life - Diabetic Neuropathy (QoL-DN) Domain Scores: Change from Baseline to Month 18, MMRM Model
Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A) Subgroup Analysis
mITT Population

Norfolk QoL-DN Domain: Physical Functioning/Large Fiber

Subgroup Visit	LS Mean (95% CI) Vutrisiran (HELIOS-A) (N=122)	LS Mean (95% CI) Patisiran (HELIOS-A) (N=42)	LS Mean Difference (Vutrisiran-Patisiran) (95% CI), p-value	Standardized Effect Size (95% CI)
Genotype				
V30M	52	20		
Month 9	-2.57 (-5.22, 0.08)	-2.18 (-6.45, 2.09)	-0.39 (-5.43, 4.64), 0.8780	-0.05 (-0.56, 0.46)
Month 18	-1.93 (-4.69, 0.82)	-2.58 (-7.04, 1.88)	0.65 (-4.60, 5.90), 0.8076	0.07 (-0.44, 0.58)
non-V30M	65	20		
Month 9	-3.09 (-5.46, -0.72)	2.47 (-1.81, 6.74)	-5.56 (-10.45, -0.66), 0.0264	-0.50 (-1.00, 0.01)
Month 18	-2.45 (-4.95, 0.05)	2.07 (-2.45, 6.58)	-4.52 (-9.68, 0.65), 0.0863	-0.38 (-0.90, 0.14)
p-value of Treatment*Genotype	0.1424			

Norfolk QoL-DN score = composite of 35 quality of life questions; lower scores indicate higher quality of life (range = -4 to 136). Nonmissing scores for items 27-33 imputed for patients who reported an impact due to COVID-19 pandemic. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.
LS estimates and p-value derived from mixed-effects model for repeated measures (MMRM), controlling for categorical factors (treatment, visit), the subgroup variable, continuous covariate (baseline value), and interaction (treatment by visit, treatment by subgroup).
Standardized effect size (d) = LS mean difference/estimated pooled standard deviation with the small sample bias correction.

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Table 3.5
Norfolk Quality of Life - Diabetic Neuropathy (QoL-DN) Domain Scores: Change from Baseline to Month 18, MMRM Model
Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A) Subgroup Analysis
mITT Population

Norfolk QoL-DN Domain: Physical Functioning/Large Fiber

Subgroup Visit	LS Mean (95% CI) Vutrisiran (HELIOS-A) (N=122)	LS Mean (95% CI) Patisiran (HELIOS-A) (N=42)	LS Mean Difference (Vutrisiran-Patisiran) (95% CI), p-value	Standardized Effect Size (95% CI)
FAP Stage				
I	82	30		
Month 9	-5.58 (-7.61, -3.54)	-1.94 (-5.28, 1.40)	-3.64 (-7.50, 0.23), 0.0651	-0.44 (-0.86, -0.02)
Month 18	-4.93 (-7.06, -2.81)	-2.31 (-5.81, 1.19)	-2.62 (-6.68, 1.43), 0.2031	-0.28 (-0.69, 0.14)
II&III	35	10		
Month 9	3.34 (0.26, 6.41)	6.15 (0.46, 11.83)	-2.81 (-9.16, 3.53), 0.3828	-0.25 (-0.94, 0.45)
Month 18	3.98 (0.84, 7.11)	5.78 (-0.07, 11.63)	-1.80 (-8.33, 4.73), 0.5868	-0.16 (-0.92, 0.59)
p-value of Treatment*FAP Stage	0.8236			

Norfolk QoL-DN score = composite of 35 quality of life questions; lower scores indicate higher quality of life (range = -4 to 136). Nonmissing scores for items 27-33 imputed for patients who reported an impact due to COVID-19 pandemic. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.
LS estimates and p-value derived from mixed-effects model for repeated measures (MMRM), controlling for categorical factors (treatment, visit), the subgroup variable, continuous covariate (baseline value), and interaction (treatment by visit, treatment by subgroup).
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Table 3.5
Norfolk Quality of Life - Diabetic Neuropathy (QoL-DN) Domain Scores: Change from Baseline to Month 18, MMRM Model
Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A) Subgroup Analysis
mITT Population

Norfolk QoL-DN Domain: Physical Functioning/Large Fiber

Subgroup Visit	LS Mean (95% CI) Vutrisiran (HELIOS-A) (N=122)	LS Mean (95% CI) Patisiran (HELIOS-A) (N=42)	LS Mean Difference (Vutrisiran-Patisiran) (95% CI), p-value	Standardized Effect Size (95% CI)
Cardiac Subpopulation				
Yes	38	14		
Month 9	-1.64 (-4.67, 1.39)	5.60 (0.60, 10.61)	-7.24 (-13.08, -1.41), 0.0153	-0.64 (-1.26, -0.03)
Month 18	-1.00 (-4.11, 2.11)	5.19 (0.03, 10.34)	-6.18 (-12.19, -0.18), 0.0436	-0.51 (-1.14, 0.12)
No	79	26		
Month 9	-3.48 (-5.63, -1.33)	-2.83 (-6.55, 0.90)	-0.65 (-4.94, 3.64), 0.7647	-0.07 (-0.51, 0.37)
Month 18	-2.84 (-5.09, -0.59)	-3.25 (-7.16, 0.67)	0.41 (-4.09, 4.91), 0.8580	0.04 (-0.41, 0.49)
p-value of Treatment*Cardiac Subpopulation	0.0679			

Norfolk QoL-DN score = composite of 35 quality of life questions; lower scores indicate higher quality of life (range = -4 to 136). Nonmissing scores for items 27-33 imputed for patients who reported an impact due to COVID-19 pandemic. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.
LS estimates and p-value derived from mixed-effects model for repeated measures (MMRM), controlling for categorical factors (treatment, visit), the subgroup variable, continuous covariate (baseline value), and interaction (treatment by visit, treatment by subgroup).
Standardized effect size (d) = LS mean difference/estimated pooled standard deviation with the small sample bias correction.

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

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Table 3.5
Norfolk Quality of Life - Diabetic Neuropathy (QoL-DN) Domain Scores: Change from Baseline to Month 18, MMRM Model
Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A) Subgroup Analysis
mITT Population

Norfolk QoL-DN Domain: Physical Functioning/Large Fiber

Subgroup Visit	LS Mean (95% CI) Vutrisiran (HELIOS-A) (N=122)	LS Mean (95% CI) Patisiran (HELIOS-A) (N=42)	LS Mean Difference (Vutrisiran-Patisiran) (95% CI), p-value	Standardized Effect Size (95% CI)
Weight (kg)				
<65	44	15		
Month 9	-1.89 (-4.77, 0.98)	0.60 (-4.32, 5.53)	-2.50 (-8.20, 3.20), 0.3880	-0.25 (-0.83, 0.33)
Month 18	-1.25 (-4.22, 1.72)	0.17 (-4.90, 5.24)	-1.42 (-7.30, 4.46), 0.6337	-0.13 (-0.72, 0.45)
≥65	73	25		
Month 9	-3.46 (-5.73, -1.19)	-0.15 (-4.00, 3.71)	-3.31 (-7.78, 1.16), 0.1458	-0.34 (-0.79, 0.12)
Month 18	-2.81 (-5.19, -0.43)	-0.58 (-4.66, 3.51)	-2.23 (-6.96, 2.49), 0.3521	-0.21 (-0.68, 0.26)
p-value of Treatment*Weight	0.8219			

Norfolk QoL-DN score = composite of 35 quality of life questions; lower scores indicate higher quality of life (range = -4 to 136). Nonmissing scores for items 27-33 imputed for patients who reported an impact due to COVID-19 pandemic. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.
LS estimates and p-value derived from mixed-effects model for repeated measures (MMRM), controlling for categorical factors (treatment, visit), the subgroup variable, continuous covariate (baseline value), and interaction (treatment by visit, treatment by subgroup).
Standardized effect size (d) = LS mean difference/estimated pooled standard deviation with the small sample bias correction.

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

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Table 3.8
Norfolk Quality of Life - Diabetic Neuropathy (QoL-DN) Domain Scores: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Norfolk QoL-DN Domain: Physical Functioning/Large Fiber

Age (years): <65

Subgroup Visit	Vutrisiran (HELIOS-A) (N=76)	Patisiran (HELIOS-A) (N=31)
Baseline		
n	75	31
Mean (SD)	22.1 (14.2)	22.4 (14.1)
SE	1.6	2.5
Median	20.0	24.0
Min, Max	-1, 51	0, 51
Month 9		
Actual Value		
n	74	30
Mean (SD)	19.9 (13.9)	21.9 (13.4)
SE	1.6	2.5
Median	20.0	23.0
Min, Max	-4, 50	0, 50
Change from baseline		
n	73	30
Mean (SD)	-1.7 (10.9)	0.4 (10.6)
SE	1.3	1.9
Median	-2.0	0.0
Min, Max	-30, 27	-15, 31

Norfolk QoL-DN score = composite of 35 quality of life questions; lower scores indicate higher quality of life (range = -4 to 136). Nonmissing scores for items 27-33 imputed for patients who reported an impact due to COVID-19 pandemic. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

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Table 3.8
Norfolk Quality of Life - Diabetic Neuropathy (QoL-DN) Domain Scores: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Norfolk QoL-DN Domain: Physical Functioning/Large Fiber

Age (years): <65

Subgroup Visit	Vutrisiran (HELIOS-A) (N=76)	Patisiran (HELIOS-A) (N=31)
Month 18		
Actual Value		
n	74	29
Mean (SD)	19.1 (14.1)	20.5 (14.0)
SE	1.6	2.6
Median	18.5	20.0
Min, Max	-2, 49	0, 47
Change from baseline		
n	73	29
Mean (SD)	-2.6 (12.3)	0.1 (11.1)
SE	1.4	2.1
Median	-3.0	-1.0
Min, Max	-34, 24	-21, 31

Norfolk QoL-DN score = composite of 35 quality of life questions; lower scores indicate higher quality of life (range = -4 to 136). Nonmissing scores for items 27-33 imputed for patients who reported an impact due to COVID-19 pandemic. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

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Table 3.8
Norfolk Quality of Life - Diabetic Neuropathy (QoL-DN) Domain Scores: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Norfolk QoL-DN Domain: Physical Functioning/Large Fiber

Age (years): ≥65

Subgroup Visit	Vutrisiran (HELIOS-A) (N=46)	Patisiran (HELIOS-A) (N=11)
Baseline		
n	46	11
Mean (SD)	24.9 (13.0)	24.8 (17.3)
SE	1.9	5.2
Median	23.5	29.0
Min, Max	0, 52	-2, 51
Month 9		
Actual Value		
n	42	10
Mean (SD)	19.2 (13.2)	26.0 (13.6)
SE	2.0	4.3
Median	19.5	27.0
Min, Max	-1, 48	9, 54
Change from baseline		
n	42	10
Mean (SD)	-4.5 (10.7)	0.1 (12.6)
SE	1.7	4.0
Median	-2.0	-2.5
Min, Max	-32, 17	-14, 25

Norfolk QoL-DN score = composite of 35 quality of life questions; lower scores indicate higher quality of life (range = -4 to 136). Nonmissing scores for items 27-33 imputed for patients who reported an impact due to COVID-19 pandemic. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

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Table 3.8
Norfolk Quality of Life - Diabetic Neuropathy (QoL-DN) Domain Scores: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Norfolk QoL-DN Domain: Physical Functioning/Large Fiber

Age (years): ≥65

Subgroup Visit	Vutrisiran (HELIOS-A) (N=46)	Patisiran (HELIOS-A) (N=11)
Month 18		
Actual Value		
n	40	9
Mean (SD)	22.4 (13.2)	26.0 (16.5)
SE	2.1	5.5
Median	22.5	31.0
Min, Max	-1, 50	4, 49
Change from baseline		
n	40	9
Mean (SD)	-1.0 (11.0)	0.6 (9.9)
SE	1.7	3.3
Median	-1.0	-1.0
Min, Max	-22, 36	-10, 20

Norfolk QoL-DN score = composite of 35 quality of life questions; lower scores indicate higher quality of life (range = -4 to 136). Nonmissing scores for items 27-33 imputed for patients who reported an impact due to COVID-19 pandemic. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

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Table 3.8
Norfolk Quality of Life - Diabetic Neuropathy (QoL-DN) Domain Scores: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Norfolk QoL-DN Domain: Physical Functioning/Large Fiber

Sex: Male

Subgroup Visit	Vutrisiran (HELIOS-A) (N=79)	Patisiran (HELIOS-A) (N=27)
Baseline		
n	78	27
Mean (SD)	23.2 (13.7)	23.4 (14.5)
SE	1.5	2.8
Median	21.0	27.0
Min, Max	-1, 51	-2, 51
Month 9		
Actual Value		
n	76	25
Mean (SD)	19.8 (13.5)	22.9 (14.6)
SE	1.5	2.9
Median	19.0	23.0
Min, Max	-4, 50	0, 54
Change from baseline		
n	75	25
Mean (SD)	-2.9 (11.4)	0.1 (11.7)
SE	1.3	2.3
Median	-2.0	-1.0
Min, Max	-32, 27	-15, 31

Norfolk QoL-DN score = composite of 35 quality of life questions; lower scores indicate higher quality of life (range = -4 to 136). Nonmissing scores for items 27-33 imputed for patients who reported an impact due to COVID-19 pandemic. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

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Table 3.8
Norfolk Quality of Life - Diabetic Neuropathy (QoL-DN) Domain Scores: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Norfolk QoL-DN Domain: Physical Functioning/Large Fiber

Sex: Male

Subgroup Visit	Vutrisiran (HELIOS-A) (N=79)	Patisiran (HELIOS-A) (N=27)
Month 18		
Actual Value		
n	74	23
Mean (SD)	20.7 (13.9)	20.8 (14.7)
SE	1.6	3.1
Median	19.0	20.0
Min, Max	-2, 50	3, 49
Change from baseline		
n	73	23
Mean (SD)	-1.8 (12.9)	-0.4 (10.2)
SE	1.5	2.1
Median	-2.0	-2.0
Min, Max	-34, 36	-15, 28

Norfolk QoL-DN score = composite of 35 quality of life questions; lower scores indicate higher quality of life (range = -4 to 136). Nonmissing scores for items 27-33 imputed for patients who reported an impact due to COVID-19 pandemic. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 3.8
Norfolk Quality of Life - Diabetic Neuropathy (QoL-DN) Domain Scores: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Norfolk QoL-DN Domain: Physical Functioning/Large Fiber

Sex: Female

Subgroup Visit	Vutrisiran (HELIOS-A) (N=43)	Patisiran (HELIOS-A) (N=15)
Baseline		
n	43	15
Mean (SD)	23.2 (14.2)	22.3 (15.9)
SE	2.2	4.1
Median	22.0	24.0
Min, Max	-1, 52	0, 51
Month 9		
Actual Value		
n	40	15
Mean (SD)	19.3 (14.0)	22.9 (11.7)
SE	2.2	3.0
Median	22.5	23.0
Min, Max	-2, 45	0, 42
Change from baseline		
n	40	15
Mean (SD)	-2.6 (9.8)	0.7 (9.9)
SE	1.6	2.6
Median	-1.0	0.0
Min, Max	-26, 19	-14, 18

Norfolk QoL-DN score = composite of 35 quality of life questions; lower scores indicate higher quality of life (range = -4 to 136). Nonmissing scores for items 27-33 imputed for patients who reported an impact due to COVID-19 pandemic. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

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Table 3.8
Norfolk Quality of Life - Diabetic Neuropathy (QoL-DN) Domain Scores: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Norfolk QoL-DN Domain: Physical Functioning/Large Fiber

Sex: Female

Subgroup Visit	Vutrisiran (HELIOS-A) (N=43)	Patisiran (HELIOS-A) (N=15)
Month 18		
Actual Value		
n	40	15
Mean (SD)	19.4 (13.9)	23.4 (14.7)
SE	2.2	3.8
Median	20.0	23.0
Min, Max	-1, 43	0, 47
Change from baseline		
n	40	15
Mean (SD)	-2.6 (9.7)	1.1 (11.8)
SE	1.5	3.0
Median	-3.5	0.0
Min, Max	-20, 21	-21, 31

Norfolk QoL-DN score = composite of 35 quality of life questions; lower scores indicate higher quality of life (range = -4 to 136). Nonmissing scores for items 27-33 imputed for patients who reported an impact due to COVID-19 pandemic. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 3.8
Norfolk Quality of Life - Diabetic Neuropathy (QoL-DN) Domain Scores: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Norfolk QoL-DN Domain: Physical Functioning/Large Fiber

Race: White

Subgroup Visit	Vutrisiran (HELIOS-A) (N=86)	Patisiran (HELIOS-A) (N=29)
Baseline		
n	85	29
Mean (SD)	22.8 (14.6)	24.3 (15.0)
SE	1.6	2.8
Median	20.0	26.0
Min, Max	-1, 52	-2, 51
Month 9		
Actual Value		
n	82	28
Mean (SD)	20.6 (13.5)	24.4 (12.6)
SE	1.5	2.4
Median	21.0	23.5
Min, Max	-2, 50	1, 50
Change from baseline		
n	81	28
Mean (SD)	-1.3 (9.4)	-0.3 (10.8)
SE	1.0	2.0
Median	0.0	-1.0
Min, Max	-27, 19	-15, 31

Norfolk QoL-DN score = composite of 35 quality of life questions; lower scores indicate higher quality of life (range = -4 to 136). Nonmissing scores for items 27-33 imputed for patients who reported an impact due to COVID-19 pandemic. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 3.8
Norfolk Quality of Life - Diabetic Neuropathy (QoL-DN) Domain Scores: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Norfolk QoL-DN Domain: Physical Functioning/Large Fiber

Race: White

Subgroup Visit	Vutrisiran (HELIOS-A) (N=86)	Patisiran (HELIOS-A) (N=29)
Month 18		
Actual Value		
n	81	27
Mean (SD)	20.3 (13.9)	23.3 (14.8)
SE	1.5	2.9
Median	19.0	23.0
Min, Max	-1, 49	3, 47
Change from baseline		
n	80	27
Mean (SD)	-2.0 (11.6)	-0.4 (11.4)
SE	1.3	2.2
Median	-2.0	-2.0
Min, Max	-34, 26	-21, 31

Norfolk QoL-DN score = composite of 35 quality of life questions; lower scores indicate higher quality of life (range = -4 to 136). Nonmissing scores for items 27-33 imputed for patients who reported an impact due to COVID-19 pandemic. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

Alnylam Pharmaceuticals Inc.
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Table 3.8
Norfolk Quality of Life - Diabetic Neuropathy (QoL-DN) Domain Scores: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Norfolk QoL-DN Domain: Physical Functioning/Large Fiber

Race: All Other Races

Subgroup Visit	Vutrisiran (HELIOS-A) (N=36)	Patisiran (HELIOS-A) (N=13)
Baseline		
n	36	13
Mean (SD)	24.0 (11.8)	20.1 (14.6)
SE	2.0	4.1
Median	22.0	24.0
Min, Max	-1, 46	0, 49
Month 9		
Actual Value		
n	34	12
Mean (SD)	17.3 (13.7)	19.5 (15.2)
SE	2.3	4.4
Median	14.5	22.0
Min, Max	-4, 45	0, 54
Change from baseline		
n	34	12
Mean (SD)	-6.2 (13.2)	1.8 (11.5)
SE	2.3	3.3
Median	-5.0	0.0
Min, Max	-32, 27	-14, 25

Norfolk QoL-DN score = composite of 35 quality of life questions; lower scores indicate higher quality of life (range = -4 to 136). Nonmissing scores for items 27-33 imputed for patients who reported an impact due to COVID-19 pandemic. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

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Table 3.8
Norfolk Quality of Life - Diabetic Neuropathy (QoL-DN) Domain Scores: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Norfolk QoL-DN Domain: Physical Functioning/Large Fiber

Race: All Other Races

Subgroup Visit	Vutrisiran (HELIOS-A) (N=36)	Patisiran (HELIOS-A) (N=13)
Month 18		
Actual Value		
n	33	11
Mean (SD)	20.2 (13.9)	18.2 (13.8)
SE	2.4	4.2
Median	19.0	21.0
Min, Max	-2, 50	0, 49
Change from baseline		
n	33	11
Mean (SD)	-2.3 (12.5)	1.6 (9.3)
SE	2.2	2.8
Median	-3.0	0.0
Min, Max	-22, 36	-10, 20

Norfolk QoL-DN score = composite of 35 quality of life questions; lower scores indicate higher quality of life (range = -4 to 136). Nonmissing scores for items 27-33 imputed for patients who reported an impact due to COVID-19 pandemic. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

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Table 3.8
Norfolk Quality of Life - Diabetic Neuropathy (QoL-DN) Domain Scores: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Norfolk QoL-DN Domain: Physical Functioning/Large Fiber

Region: North America

Subgroup Visit	Vutrisiran (HELIOS-A) (N=27)	Patisiran (HELIOS-A) (N=8)
Baseline		
n	26	8
Mean (SD)	21.3 (14.4)	23.6 (12.5)
SE	2.8	4.4
Median	17.5	23.5
Min, Max	-1, 46	9, 41
Month 9		
Actual Value		
n	25	8
Mean (SD)	14.6 (11.1)	23.1 (17.9)
SE	2.2	6.3
Median	11.0	20.5
Min, Max	-1, 39	1, 54
Change from baseline		
n	24	8
Mean (SD)	-5.6 (10.9)	-0.5 (12.2)
SE	2.2	4.3
Median	-2.5	-3.5
Min, Max	-30, 11	-13, 25

Norfolk QoL-DN score = composite of 35 quality of life questions; lower scores indicate higher quality of life (range = -4 to 136). Nonmissing scores for items 27-33 imputed for patients who reported an impact due to COVID-19 pandemic. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

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Table 3.8
Norfolk Quality of Life - Diabetic Neuropathy (QoL-DN) Domain Scores: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Norfolk QoL-DN Domain: Physical Functioning/Large Fiber

Region: North America

Subgroup Visit	Vutrisiran (HELIOS-A) (N=27)	Patisiran (HELIOS-A) (N=8)
Month 18		
Actual Value		
n	25	7
Mean (SD)	15.2 (13.4)	18.6 (17.5)
SE	2.7	6.6
Median	12.0	12.0
Min, Max	0, 50	3, 49
Change from baseline		
n	24	7
Mean (SD)	-5.2 (15.5)	-4.1 (13.2)
SE	3.2	5.0
Median	-6.5	-5.0
Min, Max	-34, 36	-21, 20

Norfolk QoL-DN score = composite of 35 quality of life questions; lower scores indicate higher quality of life (range = -4 to 136). Nonmissing scores for items 27-33 imputed for patients who reported an impact due to COVID-19 pandemic. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 3.8
Norfolk Quality of Life - Diabetic Neuropathy (QoL-DN) Domain Scores: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Norfolk QoL-DN Domain: Physical Functioning/Large Fiber

Region: Western Europe

Subgroup Visit	Vutrisiran (HELIOS-A) (N=42)	Patisiran (HELIOS-A) (N=20)
Baseline		
n	42	20
Mean (SD)	23.7 (14.9)	24.6 (15.5)
SE	2.3	3.5
Median	20.0	26.5
Min, Max	0, 52	-2, 51
Month 9		
Actual Value		
n	39	18
Mean (SD)	21.3 (14.1)	20.8 (8.0)
SE	2.3	1.9
Median	21.0	22.0
Min, Max	-1, 50	9, 37
Change from baseline		
n	39	18
Mean (SD)	-1.5 (11.6)	-2.9 (9.8)
SE	1.9	2.3
Median	-1.0	-2.5
Min, Max	-26, 19	-15, 12

Norfolk QoL-DN score = composite of 35 quality of life questions; lower scores indicate higher quality of life (range = -4 to 136). Nonmissing scores for items 27-33 imputed for patients who reported an impact due to COVID-19 pandemic. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

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Table 3.8
Norfolk Quality of Life - Diabetic Neuropathy (QoL-DN) Domain Scores: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Norfolk QoL-DN Domain: Physical Functioning/Large Fiber

Region: Western Europe

Subgroup Visit	Vutrisiran (HELIOS-A) (N=42)	Patisiran (HELIOS-A) (N=20)
Month 18		
Actual Value		
n	39	18
Mean (SD)	21.5 (13.1)	21.6 (11.9)
SE	2.1	2.8
Median	21.0	22.0
Min, Max	-1, 45	4, 44
Change from baseline		
n	39	18
Mean (SD)	-1.3 (11.1)	-2.2 (6.2)
SE	1.8	1.5
Median	-4.0	-2.5
Min, Max	-19, 26	-13, 10

Norfolk QoL-DN score = composite of 35 quality of life questions; lower scores indicate higher quality of life (range = -4 to 136). Nonmissing scores for items 27-33 imputed for patients who reported an impact due to COVID-19 pandemic. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

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Table 3.8
Norfolk Quality of Life - Diabetic Neuropathy (QoL-DN) Domain Scores: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Norfolk QoL-DN Domain: Physical Functioning/Large Fiber

Region: Rest of World

Subgroup Visit	Vutrisiran (HELIOS-A) (N=53)	Patisiran (HELIOS-A) (N=14)
Baseline		
n	53	14
Mean (SD)	23.7 (12.7)	20.4 (15.7)
SE	1.8	4.2
Median	22.0	15.5
Min, Max	-1, 46	0, 51
Month 9		
Actual Value		
n	52	14
Mean (SD)	20.9 (13.9)	25.4 (16.5)
SE	1.9	4.4
Median	22.5	26.0
Min, Max	-4, 45	0, 50
Change from baseline		
n	52	14
Mean (SD)	-2.4 (10.3)	5.0 (10.7)
SE	1.4	2.8
Median	-1.5	1.5
Min, Max	-32, 27	-7, 31

Norfolk QoL-DN score = composite of 35 quality of life questions; lower scores indicate higher quality of life (range = -4 to 136). Nonmissing scores for items 27-33 imputed for patients who reported an impact due to COVID-19 pandemic. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

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Table 3.8
Norfolk Quality of Life - Diabetic Neuropathy (QoL-DN) Domain Scores: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Norfolk QoL-DN Domain: Physical Functioning/Large Fiber

Region: Rest of World

Subgroup Visit	Vutrisiran (HELIOS-A) (N=53)	Patisiran (HELIOS-A) (N=14)
Month 18		
Actual Value		
n	50	13
Mean (SD)	21.9 (14.3)	23.9 (17.0)
SE	2.0	4.7
Median	23.0	23.0
Min, Max	-2, 49	0, 47
Change from baseline		
n	50	13
Mean (SD)	-1.2 (10.3)	5.8 (12.6)
SE	1.5	3.5
Median	-1.0	2.0
Min, Max	-24, 24	-10, 31

Norfolk QoL-DN score = composite of 35 quality of life questions; lower scores indicate higher quality of life (range = -4 to 136). Nonmissing scores for items 27-33 imputed for patients who reported an impact due to COVID-19 pandemic. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 3.8
Norfolk Quality of Life - Diabetic Neuropathy (QoL-DN) Domain Scores: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Norfolk QoL-DN Domain: Physical Functioning/Large Fiber

Baseline NIS: <50

Subgroup Visit	Vutrisiran (HELIOS-A) (N=78)	Patisiran (HELIOS-A) (N=27)
Baseline		
n	77	27
Mean (SD)	18.9 (13.3)	17.7 (13.2)
SE	1.5	2.5
Median	18.0	14.0
Min, Max	-1, 51	-2, 42
Month 9		
Actual Value		
n	77	27
Mean (SD)	13.7 (11.1)	18.4 (12.2)
SE	1.3	2.3
Median	12.0	19.0
Min, Max	-4, 39	0, 54
Change from baseline		
n	76	27
Mean (SD)	-4.7 (10.7)	0.7 (10.1)
SE	1.2	1.9
Median	-2.5	0.0
Min, Max	-32, 19	-14, 25

Norfolk QoL-DN score = composite of 35 quality of life questions; lower scores indicate higher quality of life (range = -4 to 136). Nonmissing scores for items 27-33 imputed for patients who reported an impact due to COVID-19 pandemic. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 3.8
Norfolk Quality of Life - Diabetic Neuropathy (QoL-DN) Domain Scores: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Norfolk QoL-DN Domain: Physical Functioning/Large Fiber

Baseline NIS: <50

Subgroup Visit	Vutrisiran (HELIOS-A) (N=78)	Patisiran (HELIOS-A) (N=27)
Month 18		
Actual Value		
n	75	26
Mean (SD)	14.3 (11.9)	16.5 (13.2)
SE	1.4	2.6
Median	12.0	12.0
Min, Max	-2, 50	0, 49
Change from baseline		
n	74	26
Mean (SD)	-3.8 (11.9)	-0.7 (10.6)
SE	1.4	2.1
Median	-4.0	-0.5
Min, Max	-34, 36	-21, 31

Norfolk QoL-DN score = composite of 35 quality of life questions; lower scores indicate higher quality of life (range = -4 to 136). Nonmissing scores for items 27-33 imputed for patients who reported an impact due to COVID-19 pandemic. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 3.8
Norfolk Quality of Life - Diabetic Neuropathy (QoL-DN) Domain Scores: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Norfolk QoL-DN Domain: Physical Functioning/Large Fiber

Baseline NIS: ≥50

Subgroup Visit	Vutrisiran (HELIOS-A) (N=44)	Patisiran (HELIOS-A) (N=15)
Baseline		
n	44	15
Mean (SD)	30.7 (11.2)	32.5 (13.2)
SE	1.7	3.4
Median	30.5	34.0
Min, Max	10, 52	7, 51
Month 9		
Actual Value		
n	39	13
Mean (SD)	31.4 (10.1)	32.3 (11.1)
SE	1.6	3.1
Median	31.0	30.0
Min, Max	10, 50	10, 50
Change from baseline		
n	39	13
Mean (SD)	1.1 (10.2)	-0.4 (12.9)
SE	1.6	3.6
Median	1.0	-1.0
Min, Max	-19, 27	-15, 31

Norfolk QoL-DN score = composite of 35 quality of life questions; lower scores indicate higher quality of life (range = -4 to 136). Nonmissing scores for items 27-33 imputed for patients who reported an impact due to COVID-19 pandemic. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 3.8
Norfolk Quality of Life - Diabetic Neuropathy (QoL-DN) Domain Scores: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Norfolk QoL-DN Domain: Physical Functioning/Large Fiber

Baseline NIS: ≥50

Subgroup Visit	Vutrisiran (HELIOS-A) (N=44)	Patisiran (HELIOS-A) (N=15)
Month 18		
Actual Value		
n	39	12
Mean (SD)	31.6 (9.4)	33.3 (10.3)
SE	1.5	3.0
Median	32.0	32.5
Min, Max	4, 49	21, 47
Change from baseline		
n	39	12
Mean (SD)	1.3 (11.1)	2.1 (11.2)
SE	1.8	3.2
Median	1.0	-3.5
Min, Max	-24, 26	-10, 28

Norfolk QoL-DN score = composite of 35 quality of life questions; lower scores indicate higher quality of life (range = -4 to 136). Nonmissing scores for items 27-33 imputed for patients who reported an impact due to COVID-19 pandemic. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 3.8
Norfolk Quality of Life - Diabetic Neuropathy (QoL-DN) Domain Scores: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Norfolk QoL-DN Domain: Physical Functioning/Large Fiber

Previous Tetramer Stabilizer Use: Yes

Subgroup Visit	Vutrisiran (HELIOS-A) (N=75)	Patisiran (HELIOS-A) (N=33)
Baseline		
n	75	33
Mean (SD)	21.7 (13.1)	24.3 (15.3)
SE	1.5	2.7
Median	19.0	27.0
Min, Max	0, 52	-2, 51
Month 9		
Actual Value		
n	74	32
Mean (SD)	20.5 (13.2)	23.5 (12.1)
SE	1.5	2.1
Median	20.5	23.0
Min, Max	-1, 50	0, 50
Change from baseline		
n	74	32
Mean (SD)	-1.0 (10.0)	-0.1 (10.2)
SE	1.2	1.8
Median	-1.0	-0.5
Min, Max	-32, 27	-15, 31

Norfolk QoL-DN score = composite of 35 quality of life questions; lower scores indicate higher quality of life (range = -4 to 136). Nonmissing scores for items 27-33 imputed for patients who reported an impact due to COVID-19 pandemic. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 3.8
Norfolk Quality of Life - Diabetic Neuropathy (QoL-DN) Domain Scores: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Norfolk QoL-DN Domain: Physical Functioning/Large Fiber

Previous Tetramer Stabilizer Use: Yes

Subgroup Visit	Vutrisiran (HELIOS-A) (N=75)	Patisiran (HELIOS-A) (N=33)
Month 18		
Actual Value		
n	71	31
Mean (SD)	20.8 (13.6)	22.1 (13.2)
SE	1.6	2.4
Median	20.0	21.0
Min, Max	-1, 49	4, 47
Change from baseline		
n	71	31
Mean (SD)	-0.5 (10.7)	-0.6 (9.3)
SE	1.3	1.7
Median	-2.0	-1.0
Min, Max	-31, 26	-21, 28

Norfolk QoL-DN score = composite of 35 quality of life questions; lower scores indicate higher quality of life (range = -4 to 136). Nonmissing scores for items 27-33 imputed for patients who reported an impact due to COVID-19 pandemic. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 3.8
Norfolk Quality of Life - Diabetic Neuropathy (QoL-DN) Domain Scores: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Norfolk QoL-DN Domain: Physical Functioning/Large Fiber

Previous Tetramer Stabilizer Use: No

Subgroup Visit	Vutrisiran (HELIOS-A) (N=47)	Patisiran (HELIOS-A) (N=9)
Baseline		
n	46	9
Mean (SD)	25.6 (14.7)	18.1 (12.8)
SE	2.2	4.3
Median	23.5	14.0
Min, Max	-1, 51	0, 41
Month 9		
Actual Value		
n	42	8
Mean (SD)	18.2 (14.3)	20.6 (18.5)
SE	2.2	6.5
Median	17.0	22.0
Min, Max	-4, 48	0, 54
Change from baseline		
n	41	8
Mean (SD)	-5.8 (11.7)	2.0 (14.1)
SE	1.8	5.0
Median	-5.0	-3.5
Min, Max	-30, 17	-13, 25

Norfolk QoL-DN score = composite of 35 quality of life questions; lower scores indicate higher quality of life (range = -4 to 136). Nonmissing scores for items 27-33 imputed for patients who reported an impact due to COVID-19 pandemic. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 3.8
Norfolk Quality of Life - Diabetic Neuropathy (QoL-DN) Domain Scores: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Norfolk QoL-DN Domain: Physical Functioning/Large Fiber

Previous Tetramer Stabilizer Use: No

Subgroup Visit	Vutrisiran (HELIOS-A) (N=47)	Patisiran (HELIOS-A) (N=9)
Month 18		
Actual Value		
n	43	7
Mean (SD)	19.4 (14.4)	20.7 (20.9)
SE	2.2	7.9
Median	18.0	12.0
Min, Max	-2, 50	0, 49
Change from baseline		
n	42	7
Mean (SD)	-4.8 (13.2)	3.7 (16.2)
SE	2.0	6.1
Median	-4.0	0.0
Min, Max	-34, 36	-15, 31

Norfolk QoL-DN score = composite of 35 quality of life questions; lower scores indicate higher quality of life (range = -4 to 136). Nonmissing scores for items 27-33 imputed for patients who reported an impact due to COVID-19 pandemic. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 3.8
Norfolk Quality of Life - Diabetic Neuropathy (QoL-DN) Domain Scores: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Norfolk QoL-DN Domain: Physical Functioning/Large Fiber

Genotype: V30M

Subgroup Visit	Vutrisiran (HELIOS-A) (N=54)	Patisiran (HELIOS-A) (N=20)
Baseline		
n	53	20
Mean (SD)	21.5 (14.8)	25.6 (13.5)
SE	2.0	3.0
Median	19.0	27.0
Min, Max	-1, 51	1, 51
Month 9		
Actual Value		
n	52	20
Mean (SD)	19.0 (13.2)	22.1 (8.7)
SE	1.8	1.9
Median	20.5	23.5
Min, Max	-1, 50	4, 37
Change from baseline		
n	51	20
Mean (SD)	-2.1 (9.5)	-3.5 (9.4)
SE	1.3	2.1
Median	-1.0	-5.5
Min, Max	-30, 19	-15, 16

Norfolk QoL-DN score = composite of 35 quality of life questions; lower scores indicate higher quality of life (range = -4 to 136). Nonmissing scores for items 27-33 imputed for patients who reported an impact due to COVID-19 pandemic. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 3.8
Norfolk Quality of Life - Diabetic Neuropathy (QoL-DN) Domain Scores: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Norfolk QoL-DN Domain: Physical Functioning/Large Fiber

Genotype: V30M

Subgroup Visit	Vutrisiran (HELIOS-A) (N=54)	Patisiran (HELIOS-A) (N=20)
Month 18		
Actual Value		
n	52	20
Mean (SD)	19.4 (13.5)	23.2 (12.2)
SE	1.9	2.7
Median	19.5	23.5
Min, Max	-1, 45	4, 44
Change from baseline		
n	51	20
Mean (SD)	-1.3 (10.8)	-2.5 (9.3)
SE	1.5	2.1
Median	-2.0	-4.0
Min, Max	-25, 26	-13, 31

Norfolk QoL-DN score = composite of 35 quality of life questions; lower scores indicate higher quality of life (range = -4 to 136). Nonmissing scores for items 27-33 imputed for patients who reported an impact due to COVID-19 pandemic. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 3.8
Norfolk Quality of Life - Diabetic Neuropathy (QoL-DN) Domain Scores: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Norfolk QoL-DN Domain: Physical Functioning/Large Fiber

Genotype: non-V30M

Subgroup Visit	Vutrisiran (HELIOS-A) (N=68)	Patisiran (HELIOS-A) (N=22)
Baseline		
n	68	22
Mean (SD)	24.5 (12.9)	20.6 (15.9)
SE	1.6	3.4
Median	22.0	18.5
Min, Max	-1, 52	-2, 51
Month 9		
Actual Value		
n	64	20
Mean (SD)	20.2 (14.0)	23.7 (17.1)
SE	1.7	3.8
Median	19.0	23.0
Min, Max	-4, 45	0, 54
Change from baseline		
n	64	20
Mean (SD)	-3.3 (11.9)	4.2 (11.2)
SE	1.5	2.5
Median	-2.0	1.5
Min, Max	-32, 27	-13, 31

Norfolk QoL-DN score = composite of 35 quality of life questions; lower scores indicate higher quality of life (range = -4 to 136). Nonmissing scores for items 27-33 imputed for patients who reported an impact due to COVID-19 pandemic. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 3.8
Norfolk Quality of Life - Diabetic Neuropathy (QoL-DN) Domain Scores: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Norfolk QoL-DN Domain: Physical Functioning/Large Fiber

Genotype: non-V30M

Subgroup Visit	Vutrisiran (HELIOS-A) (N=68)	Patisiran (HELIOS-A) (N=22)
Month 18		
Actual Value		
n	62	18
Mean (SD)	21.0 (14.2)	20.3 (17.0)
SE	1.8	4.0
Median	19.0	14.5
Min, Max	-2, 50	0, 49
Change from baseline		
n	62	18
Mean (SD)	-2.7 (12.7)	3.1 (11.7)
SE	1.6	2.8
Median	-2.5	3.0
Min, Max	-34, 36	-21, 28

Norfolk QoL-DN score = composite of 35 quality of life questions; lower scores indicate higher quality of life (range = -4 to 136). Nonmissing scores for items 27-33 imputed for patients who reported an impact due to COVID-19 pandemic. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 3.8
Norfolk Quality of Life - Diabetic Neuropathy (QoL-DN) Domain Scores: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Norfolk QoL-DN Domain: Physical Functioning/Large Fiber

FAP Stage: I

Subgroup Visit	Vutrisiran (HELIOS-A) (N=84)	Patisiran (HELIOS-A) (N=31)
Baseline		
n	83	31
Mean (SD)	20.0 (13.7)	18.8 (13.8)
SE	1.5	2.5
Median	18.0	14.0
Min, Max	-1, 51	-2, 42
Month 9		
Actual Value		
n	82	30
Mean (SD)	15.4 (11.4)	19.3 (11.1)
SE	1.3	2.0
Median	15.5	20.5
Min, Max	-4, 45	0, 42
Change from baseline		
n	81	30
Mean (SD)	-4.2 (10.6)	0.3 (9.1)
SE	1.2	1.7
Median	-3.0	0.0
Min, Max	-32, 19	-14, 18

Norfolk QoL-DN score = composite of 35 quality of life questions; lower scores indicate higher quality of life (range = -4 to 136). Nonmissing scores for items 27-33 imputed for patients who reported an impact due to COVID-19 pandemic. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Norfolk Quality of Life - Diabetic Neuropathy (QoL-DN) Domain Scores: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Norfolk QoL-DN Domain: Physical Functioning/Large Fiber

FAP Stage: I

Subgroup Visit	Vutrisiran (HELIOS-A) (N=84)	Patisiran (HELIOS-A) (N=31)
Month 18		
Actual Value		
n	81	30
Mean (SD)	15.9 (12.1)	17.9 (12.8)
SE	1.3	2.3
Median	13.0	15.0
Min, Max	-2, 43	0, 47
Change from baseline		
n	80	30
Mean (SD)	-3.3 (11.4)	-1.1 (9.9)
SE	1.3	1.8
Median	-4.0	-1.0
Min, Max	-34, 26	-21, 31

Norfolk QoL-DN score = composite of 35 quality of life questions; lower scores indicate higher quality of life (range = -4 to 136). Nonmissing scores for items 27-33 imputed for patients who reported an impact due to COVID-19 pandemic. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 3.8
Norfolk Quality of Life - Diabetic Neuropathy (QoL-DN) Domain Scores: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Norfolk QoL-DN Domain: Physical Functioning/Large Fiber

FAP Stage: II&III

Subgroup Visit	Vutrisiran (HELIOS-A) (N=38)	Patisiran (HELIOS-A) (N=11)
Baseline		
n	38	11
Mean (SD)	30.1 (11.4)	34.7 (11.4)
SE	1.9	3.4
Median	31.0	30.0
Min, Max	10, 52	19, 51
Month 9		
Actual Value		
n	34	10
Mean (SD)	29.9 (13.0)	33.8 (14.5)
SE	2.2	4.6
Median	31.5	32.5
Min, Max	2, 50	10, 54
Change from baseline		
n	34	10
Mean (SD)	0.7 (10.9)	0.5 (15.9)
SE	1.9	5.0
Median	2.0	-1.0
Min, Max	-24, 27	-15, 31

Norfolk QoL-DN score = composite of 35 quality of life questions; lower scores indicate higher quality of life (range = -4 to 136). Nonmissing scores for items 27-33 imputed for patients who reported an impact due to COVID-19 pandemic. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 3.8
Norfolk Quality of Life - Diabetic Neuropathy (QoL-DN) Domain Scores: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Norfolk QoL-DN Domain: Physical Functioning/Large Fiber

FAP Stage: II&III

Subgroup Visit	Vutrisiran (HELIOS-A) (N=38)	Patisiran (HELIOS-A) (N=11)
Month 18		
Actual Value		
n	33	8
Mean (SD)	31.0 (11.9)	36.5 (11.4)
SE	2.1	4.0
Median	32.0	39.0
Min, Max	-1, 50	21, 49
Change from baseline		
n	33	8
Mean (SD)	0.9 (12.5)	5.0 (13.1)
SE	2.2	4.6
Median	-1.0	0.5
Min, Max	-22, 36	-7, 28

Norfolk QoL-DN score = composite of 35 quality of life questions; lower scores indicate higher quality of life (range = -4 to 136). Nonmissing scores for items 27-33 imputed for patients who reported an impact due to COVID-19 pandemic. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Norfolk Quality of Life - Diabetic Neuropathy (QoL-DN) Domain Scores: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Norfolk QoL-DN Domain: Physical Functioning/Large Fiber

Cardiac Subpopulation: Yes

Subgroup Visit	Vutrisiran (HELIOS-A) (N=40)	Patisiran (HELIOS-A) (N=14)
Baseline		
n	40	14
Mean (SD)	26.4 (13.4)	26.8 (17.9)
SE	2.1	4.8
Median	21.5	28.5
Min, Max	5, 48	-2, 51
Month 9		
Actual Value		
n	38	14
Mean (SD)	23.0 (13.5)	30.5 (16.1)
SE	2.2	4.3
Median	20.5	29.5
Min, Max	3, 50	0, 54
Change from baseline		
n	38	14
Mean (SD)	-2.6 (12.2)	3.7 (13.4)
SE	2.0	3.6
Median	-0.5	1.5
Min, Max	-32, 27	-14, 31

Norfolk QoL-DN score = composite of 35 quality of life questions; lower scores indicate higher quality of life (range = -4 to 136). Nonmissing scores for items 27-33 imputed for patients who reported an impact due to COVID-19 pandemic. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

Alnylam Pharmaceuticals Inc.
ALN-TTRSC02-002

Table 3.8
Norfolk Quality of Life - Diabetic Neuropathy (QoL-DN) Domain Scores: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Norfolk QoL-DN Domain: Physical Functioning/Large Fiber

Cardiac Subpopulation: Yes

Subgroup Visit	Vutrisiran (HELIOS-A) (N=40)	Patisiran (HELIOS-A) (N=14)
Month 18		
Actual Value		
n	37	13
Mean (SD)	23.7 (14.9)	30.2 (16.1)
SE	2.5	4.5
Median	23.0	32.0
Min, Max	-1, 49	6, 49
Change from baseline		
n	37	13
Mean (SD)	-2.1 (13.5)	5.3 (11.3)
SE	2.2	3.1
Median	-2.0	6.0
Min, Max	-34, 26	-10, 28

Norfolk QoL-DN score = composite of 35 quality of life questions; lower scores indicate higher quality of life (range = -4 to 136). Nonmissing scores for items 27-33 imputed for patients who reported an impact due to COVID-19 pandemic. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 3.8
Norfolk Quality of Life - Diabetic Neuropathy (QoL-DN) Domain Scores: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Norfolk QoL-DN Domain: Physical Functioning/Large Fiber

Cardiac Subpopulation: No

Subgroup Visit	Vutrisiran (HELIOS-A) (N=82)	Patisiran (HELIOS-A) (N=28)
Baseline		
n	81	28
Mean (SD)	21.6 (13.8)	21.1 (13.0)
SE	1.5	2.5
Median	21.0	21.0
Min, Max	-1, 52	0, 49
Month 9		
Actual Value		
n	78	26
Mean (SD)	18.0 (13.4)	18.8 (9.8)
SE	1.5	1.9
Median	19.5	20.5
Min, Max	-4, 45	0, 38
Change from baseline		
n	77	26
Mean (SD)	-2.8 (10.2)	-1.5 (9.1)
SE	1.2	1.8
Median	-2.0	-1.5
Min, Max	-30, 19	-15, 16

Norfolk QoL-DN score = composite of 35 quality of life questions; lower scores indicate higher quality of life (range = -4 to 136). Nonmissing scores for items 27-33 imputed for patients who reported an impact due to COVID-19 pandemic. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 3.8
Norfolk Quality of Life - Diabetic Neuropathy (QoL-DN) Domain Scores: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Norfolk QoL-DN Domain: Physical Functioning/Large Fiber

Cardiac Subpopulation: No

Subgroup Visit	Vutrisiran (HELIOS-A) (N=82)	Patisiran (HELIOS-A) (N=28)
Month 18		
Actual Value		
n	77	25
Mean (SD)	18.6 (13.1)	17.4 (11.8)
SE	1.5	2.4
Median	19.0	17.0
Min, Max	-2, 50	0, 42
Change from baseline		
n	76	25
Mean (SD)	-2.0 (11.0)	-2.5 (9.6)
SE	1.3	1.9
Median	-2.0	-3.0
Min, Max	-25, 36	-21, 31

Norfolk QoL-DN score = composite of 35 quality of life questions; lower scores indicate higher quality of life (range = -4 to 136). Nonmissing scores for items 27-33 imputed for patients who reported an impact due to COVID-19 pandemic. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 3.8
Norfolk Quality of Life - Diabetic Neuropathy (QoL-DN) Domain Scores: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Norfolk QoL-DN Domain: Physical Functioning/Large Fiber

Weight (kg): <65

Subgroup Visit	Vutrisiran (HELIOS-A) (N=46)	Patisiran (HELIOS-A) (N=15)
Baseline		
n	46	15
Mean (SD)	24.5 (14.5)	23.1 (15.1)
SE	2.1	3.9
Median	24.5	24.0
Min, Max	0, 48	1, 51
Month 9		
Actual Value		
n	44	15
Mean (SD)	21.7 (14.0)	23.0 (10.0)
SE	2.1	2.6
Median	23.0	23.0
Min, Max	-2, 50	4, 42
Change from baseline		
n	44	15
Mean (SD)	-2.0 (11.7)	-0.1 (11.4)
SE	1.8	2.9
Median	-1.0	-1.0
Min, Max	-30, 27	-15, 18

Norfolk QoL-DN score = composite of 35 quality of life questions; lower scores indicate higher quality of life (range = -4 to 136). Nonmissing scores for items 27-33 imputed for patients who reported an impact due to COVID-19 pandemic. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 3.8
Norfolk Quality of Life - Diabetic Neuropathy (QoL-DN) Domain Scores: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Norfolk QoL-DN Domain: Physical Functioning/Large Fiber

Weight (kg): <65

Subgroup Visit	Vutrisiran (HELIOS-A) (N=46)	Patisiran (HELIOS-A) (N=15)
Month 18		
Actual Value		
n	42	15
Mean (SD)	22.0 (14.3)	24.5 (14.3)
SE	2.2	3.7
Median	22.5	23.0
Min, Max	-1, 44	4, 47
Change from baseline		
n	42	15
Mean (SD)	-1.5 (11.9)	1.4 (10.5)
SE	1.8	2.7
Median	-1.5	-1.0
Min, Max	-31, 26	-10, 31

Norfolk QoL-DN score = composite of 35 quality of life questions; lower scores indicate higher quality of life (range = -4 to 136). Nonmissing scores for items 27-33 imputed for patients who reported an impact due to COVID-19 pandemic. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 3.8
Norfolk Quality of Life - Diabetic Neuropathy (QoL-DN) Domain Scores: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Norfolk QoL-DN Domain: Physical Functioning/Large Fiber

Weight (kg): ≥65

Subgroup Visit	Vutrisiran (HELIOS-A) (N=76)	Patisiran (HELIOS-A) (N=27)
Baseline		
n	75	27
Mean (SD)	22.3 (13.4)	22.9 (15.0)
SE	1.5	2.9
Median	20.0	27.0
Min, Max	-1, 52	-2, 51
Month 9		
Actual Value		
n	72	25
Mean (SD)	18.4 (13.3)	22.8 (15.3)
SE	1.6	3.1
Median	19.0	23.0
Min, Max	-4, 48	0, 54
Change from baseline		
n	71	25
Mean (SD)	-3.2 (10.3)	0.6 (10.9)
SE	1.2	2.2
Median	-2.0	0.0
Min, Max	-32, 19	-14, 31

Norfolk QoL-DN score = composite of 35 quality of life questions; lower scores indicate higher quality of life (range = -4 to 136). Nonmissing scores for items 27-33 imputed for patients who reported an impact due to COVID-19 pandemic. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 3.8
Norfolk Quality of Life - Diabetic Neuropathy (QoL-DN) Domain Scores: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Norfolk QoL-DN Domain: Physical Functioning/Large Fiber

Weight (kg): ≥65

Subgroup Visit	Vutrisiran (HELIOS-A) (N=76)	Patisiran (HELIOS-A) (N=27)
Month 18		
Actual Value		
n	72	23
Mean (SD)	19.3 (13.5)	20.0 (14.8)
SE	1.6	3.1
Median	18.0	17.0
Min, Max	-2, 50	0, 49
Change from baseline		
n	71	23
Mean (SD)	-2.4 (11.9)	-0.6 (11.0)
SE	1.4	2.3
Median	-3.0	-1.0
Min, Max	-34, 36	-21, 28

Norfolk QoL-DN score = composite of 35 quality of life questions; lower scores indicate higher quality of life (range = -4 to 136). Nonmissing scores for items 27-33 imputed for patients who reported an impact due to COVID-19 pandemic. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Norfolk-QoL-DN – Domäne Alltagsaktivitäten

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Table 3.5
Norfolk Quality of Life - Diabetic Neuropathy (QoL-DN) Domain Scores: Change from Baseline to Month 18, MMRM Model
Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A) Subgroup Analysis
mITT Population

Norfolk QoL-DN Domain: Activities of Daily Living (ADLs)

Subgroup Visit	LS Mean (95% CI) Vutrisiran (HELIOS-A) (N=122)	LS Mean (95% CI) Patisiran (HELIOS-A) (N=42)	LS Mean Difference (Vutrisiran-Patisiran) (95% CI), p-value	Standardized Effect Size (95% CI)
Age (years)				
<65	74	30		
Month 9	0.33 (-0.42, 1.08)	0.52 (-0.66, 1.70)	-0.19 (-1.59, 1.21), 0.7880	-0.06 (-0.48, 0.37)
Month 18	0.88 (-0.00, 1.77)	-0.32 (-1.76, 1.12)	1.20 (-0.48, 2.89), 0.1604	0.31 (-0.12, 0.73)
≥65	43	10		
Month 9	-0.55 (-1.53, 0.44)	1.29 (-0.74, 3.32)	-1.84 (-4.09, 0.42), 0.1098	-0.62 (-1.31, 0.07)
Month 18	0.01 (-1.09, 1.10)	0.45 (-1.74, 2.64)	-0.44 (-2.89, 2.00), 0.7224	-0.10 (-0.81, 0.61)
p-value of Treatment*Age	0.2200			

Norfolk QoL-DN score = composite of 35 quality of life questions; lower scores indicate higher quality of life (range = -4 to 136). Nonmissing scores for items 27-33 imputed for patients who reported an impact due to COVID-19 pandemic. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.
LS estimates and p-value derived from mixed-effects model for repeated measures (MMRM), controlling for categorical factors (treatment, visit), the subgroup variable, continuous covariate (baseline value), and interaction (treatment by visit, treatment by subgroup).
Standardized effect size (d) = LS mean difference/estimated pooled standard deviation with the small sample bias correction.

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

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Table 3.5
Norfolk Quality of Life - Diabetic Neuropathy (QoL-DN) Domain Scores: Change from Baseline to Month 18, MMRM Model
Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A) Subgroup Analysis
mITT Population

Norfolk QoL-DN Domain: Activities of Daily Living (ADLs)

Subgroup Visit	LS Mean (95% CI) Vutrisiran (HELIOS-A) (N=122)	LS Mean (95% CI) Patisiran (HELIOS-A) (N=42)	LS Mean Difference (Vutrisiran-Patisiran) (95% CI), p-value	Standardized Effect Size (95% CI)
Sex				
Male	76	25		
Month 9	-0.14 (-0.89, 0.60)	1.23 (-0.07, 2.52)	-1.37 (-2.86, 0.13), 0.0725	-0.39 (-0.84, 0.07)
Month 18	0.41 (-0.45, 1.28)	0.39 (-1.12, 1.90)	0.02 (-1.72, 1.77), 0.9800	0.01 (-0.46, 0.47)
Female	41	15		
Month 9	0.29 (-0.72, 1.30)	-0.15 (-1.81, 1.51)	0.44 (-1.50, 2.39), 0.6532	0.16 (-0.43, 0.75)
Month 18	0.85 (-0.26, 1.95)	-0.99 (-2.81, 0.84)	1.83 (-0.30, 3.97), 0.0913	0.51 (-0.08, 1.11)
p-value of Treatment*Sex	0.1435			

Norfolk QoL-DN score = composite of 35 quality of life questions; lower scores indicate higher quality of life (range = -4 to 136). Nonmissing scores for items 27-33 imputed for patients who reported an impact due to COVID-19 pandemic. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.
LS estimates and p-value derived from mixed-effects model for repeated measures (MMRM), controlling for categorical factors (treatment, visit), the subgroup variable, continuous covariate (baseline value), and interaction (treatment by visit, treatment by subgroup).
Standardized effect size (d) = LS mean difference/estimated pooled standard deviation with the small sample bias correction.

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Table 3.5
Norfolk Quality of Life - Diabetic Neuropathy (QoL-DN) Domain Scores: Change from Baseline to Month 18, MMRM Model
Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A) Subgroup Analysis
mITT Population

Norfolk QoL-DN Domain: Activities of Daily Living (ADLs)

Subgroup Visit	LS Mean (95% CI) Vutrisiran (HELIOS-A) (N=122)	LS Mean (95% CI) Patisiran (HELIOS-A) (N=42)	LS Mean Difference (Vutrisiran-Patisiran) (95% CI), p-value	Standardized Effect Size (95% CI)
Race				
White	82	28		
Month 9	0.17 (-0.55, 0.89)	0.59 (-0.64, 1.81)	-0.42 (-1.84, 1.00), 0.5629	-0.16 (-0.58, 0.27)
Month 18	0.73 (-0.12, 1.58)	-0.25 (-1.71, 1.21)	0.98 (-0.71, 2.67), 0.2535	0.28 (-0.15, 0.72)
All Other Races	35	12		
Month 9	-0.37 (-1.47, 0.72)	0.99 (-0.89, 2.86)	-1.36 (-3.53, 0.81), 0.2173	-0.30 (-0.95, 0.35)
Month 18	0.18 (-1.00, 1.37)	0.15 (-1.89, 2.18)	0.04 (-2.32, 2.39), 0.9759	0.01 (-0.66, 0.68)
p-value of Treatment*Race	0.4707			

Norfolk QoL-DN score = composite of 35 quality of life questions; lower scores indicate higher quality of life (range = -4 to 136). Nonmissing scores for items 27-33 imputed for patients who reported an impact due to COVID-19 pandemic. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.
LS estimates and p-value derived from mixed-effects model for repeated measures (MMRM), controlling for categorical factors (treatment, visit), the subgroup variable, continuous covariate (baseline value), and interaction (treatment by visit, treatment by subgroup).
Standardized effect size (d) = LS mean difference/estimated pooled standard deviation with the small sample bias correction.

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Table 3.5
Norfolk Quality of Life - Diabetic Neuropathy (QoL-DN) Domain Scores: Change from Baseline to Month 18, MMRM Model
Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A) Subgroup Analysis
mITT Population

Norfolk QoL-DN Domain: Activities of Daily Living (ADLs)

Subgroup Visit	LS Mean (95% CI) Vutrisiran (HELIOS-A) (N=122)	LS Mean (95% CI) Patisiran (HELIOS-A) (N=42)	LS Mean Difference (Vutrisiran-Patisiran) (95% CI), p-value	Standardized Effect Size (95% CI)
Region				
North America	26	8		
Month 9	-0.62 (-1.91, 0.67)	0.73 (-1.54, 2.99)	-1.35 (-3.94, 1.24), 0.3053	-0.39 (-1.17, 0.40)
Month 18	-0.06 (-1.42, 1.29)	-0.11 (-2.50, 2.28)	0.04 (-2.69, 2.78), 0.9744	0.01 (-0.81, 0.83)
Western Europe	39	18		
Month 9	0.08 (-0.95, 1.10)	-0.37 (-1.89, 1.14)	0.45 (-1.38, 2.28), 0.6278	0.16 (-0.39, 0.71)
Month 18	0.64 (-0.47, 1.75)	-1.21 (-2.89, 0.48)	1.84 (-0.17, 3.86), 0.0731	0.63 (0.07, 1.19)
Rest of World	52	14		
Month 9	0.26 (-0.63, 1.16)	2.06 (0.34, 3.77)	-1.79 (-3.72, 0.14), 0.0685	-0.51 (-1.10, 0.08)
Month 18	0.82 (-0.17, 1.82)	1.22 (-0.65, 3.09)	-0.40 (-2.52, 1.72), 0.7109	-0.09 (-0.70, 0.51)
p-value of Treatment*Region	0.2172			

Norfolk QoL-DN score = composite of 35 quality of life questions; lower scores indicate higher quality of life (range = -4 to 136). Nonmissing scores for items 27-33 imputed for patients who reported an impact due to COVID-19 pandemic. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.
LS estimates and p-value derived from mixed-effects model for repeated measures (MMRM), controlling for categorical factors (treatment, visit), the subgroup variable, continuous covariate (baseline value), and interaction (treatment by visit, treatment by subgroup).
Standardized effect size (d) = LS mean difference/estimated pooled standard deviation with the small sample bias correction.

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Table 3.5
Norfolk Quality of Life - Diabetic Neuropathy (QoL-DN) Domain Scores: Change from Baseline to Month 18, MMRM Model
Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A) Subgroup Analysis
mITT Population

Norfolk QoL-DN Domain: Activities of Daily Living (ADLs)

Subgroup Visit	LS Mean (95% CI) Vutrisiran (HELIOS-A) (N=122)	LS Mean (95% CI) Patisiran (HELIOS-A) (N=42)	LS Mean Difference (Vutrisiran-Patisiran) (95% CI), p-value	Standardized Effect Size (95% CI)
Baseline NIS				
<50	76	27		
Month 9	-1.34 (-2.10, -0.59)	-0.41 (-1.63, 0.81)	-0.93 (-2.29, 0.42), 0.1770	-0.34 (-0.78, 0.10)
Month 18	-0.80 (-1.65, 0.05)	-1.26 (-2.65, 0.13)	0.46 (-1.10, 2.02), 0.5636	0.13 (-0.32, 0.57)
≥50	41	13		
Month 9	2.54 (1.45, 3.64)	2.58 (0.86, 4.31)	-0.04 (-1.94, 1.87), 0.9692	-0.01 (-0.63, 0.61)
Month 18	3.08 (1.93, 4.24)	1.73 (-0.12, 3.59)	1.35 (-0.71, 3.41), 0.1968	0.34 (-0.30, 0.98)
p-value of Treatment*Baseline NIS	0.4435			

Norfolk QoL-DN score = composite of 35 quality of life questions; lower scores indicate higher quality of life (range = -4 to 136). Nonmissing scores for items 27-33 imputed for patients who reported an impact due to COVID-19 pandemic. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.
LS estimates and p-value derived from mixed-effects model for repeated measures (MMRM), controlling for categorical factors (treatment, visit), the subgroup variable, continuous covariate (baseline value), and interaction (treatment by visit, treatment by subgroup).
Standardized effect size (d) = LS mean difference/estimated pooled standard deviation with the small sample bias correction.

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Table 3.5
Norfolk Quality of Life - Diabetic Neuropathy (QoL-DN) Domain Scores: Change from Baseline to Month 18, MMRM Model
Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A) Subgroup Analysis
mITT Population

Norfolk QoL-DN Domain: Activities of Daily Living (ADLs)

Subgroup Visit	LS Mean (95% CI) Vutrisiran (HELIOS-A) (N=122)	LS Mean (95% CI) Patisiran (HELIOS-A) (N=42)	LS Mean Difference (Vutrisiran-Patisiran) (95% CI), p-value	Standardized Effect Size (95% CI)
Previous Tetramer Stabilizer Use				
Yes	74	32		
Month 9	0.10 (-0.66, 0.85)	0.52 (-0.63, 1.67)	-0.43 (-1.80, 0.95), 0.5423	-0.14 (-0.55, 0.28)
Month 18	0.65 (-0.23, 1.53)	-0.32 (-1.70, 1.07)	0.97 (-0.67, 2.61), 0.2451	0.25 (-0.17, 0.67)
No	43	8		
Month 9	-0.14 (-1.14, 0.85)	1.46 (-0.83, 3.76)	-1.60 (-4.11, 0.90), 0.2075	-0.43 (-1.18, 0.32)
Month 18	0.41 (-0.67, 1.50)	0.62 (-1.81, 3.05)	-0.21 (-2.87, 2.45), 0.8770	-0.05 (-0.83, 0.74)
p-value of Treatment*Previous Tetramer Stabilizer Use	0.4135			

Norfolk QoL-DN score = composite of 35 quality of life questions; lower scores indicate higher quality of life (range = -4 to 136). Nonmissing scores for items 27-33 imputed for patients who reported an impact due to COVID-19 pandemic. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.
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Standardized effect size (d) = LS mean difference/estimated pooled standard deviation with the small sample bias correction.

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Table 3.5
Norfolk Quality of Life - Diabetic Neuropathy (QoL-DN) Domain Scores: Change from Baseline to Month 18, MMRM Model
Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A) Subgroup Analysis
mITT Population

Norfolk QoL-DN Domain: Activities of Daily Living (ADLs)

Subgroup Visit	LS Mean (95% CI) Vutrisiran (HELIOS-A) (N=122)	LS Mean (95% CI) Patisiran (HELIOS-A) (N=42)	LS Mean Difference (Vutrisiran-Patisiran) (95% CI), p-value	Standardized Effect Size (95% CI)
Genotype				
V30M	52	20		
Month 9	-0.54 (-1.43, 0.36)	0.03 (-1.40, 1.47)	-0.57 (-2.26, 1.12), 0.5058	-0.21 (-0.72, 0.31)
Month 18	0.02 (-0.97, 1.01)	-0.80 (-2.42, 0.82)	0.82 (-1.08, 2.73), 0.3959	0.24 (-0.28, 0.75)
non-V30M	65	20		
Month 9	0.44 (-0.35, 1.24)	1.38 (-0.05, 2.82)	-0.94 (-2.58, 0.70), 0.2589	-0.26 (-0.76, 0.24)
Month 18	1.00 (0.09, 1.92)	0.55 (-1.08, 2.18)	0.45 (-1.42, 2.32), 0.6334	0.10 (-0.42, 0.62)
p-value of Treatment*Genotype	0.7553			

Norfolk QoL-DN score = composite of 35 quality of life questions; lower scores indicate higher quality of life (range = -4 to 136). Nonmissing scores for items 27-33 imputed for patients who reported an impact due to COVID-19 pandemic. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.
LS estimates and p-value derived from mixed-effects model for repeated measures (MMRM), controlling for categorical factors (treatment, visit), the subgroup variable, continuous covariate (baseline value), and interaction (treatment by visit, treatment by subgroup).
Standardized effect size (d) = LS mean difference/estimated pooled standard deviation with the small sample bias correction.

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

Alnylam Pharmaceuticals Inc.
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Table 3.5
Norfolk Quality of Life - Diabetic Neuropathy (QoL-DN) Domain Scores: Change from Baseline to Month 18, MMRM Model
Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A) Subgroup Analysis
mITT Population

Norfolk QoL-DN Domain: Activities of Daily Living (ADLs)

Subgroup Visit	LS Mean (95% CI) Vutrisiran (HELIOS-A) (N=122)	LS Mean (95% CI) Patisiran (HELIOS-A) (N=42)	LS Mean Difference (Vutrisiran-Patisiran) (95% CI), p-value	Standardized Effect Size (95% CI)
FAP Stage				
I	82	30		
Month 9	-0.97 (-1.68, -0.26)	-0.04 (-1.19, 1.10)	-0.93 (-2.24, 0.39), 0.1650	-0.32 (-0.73, 0.10)
Month 18	-0.41 (-1.22, 0.40)	-0.87 (-2.19, 0.46)	0.45 (-1.07, 1.98), 0.5575	0.14 (-0.27, 0.56)
II&III	35	10		
Month 9	2.30 (1.18, 3.42)	2.58 (0.63, 4.54)	-0.28 (-2.46, 1.89), 0.7968	-0.08 (-0.77, 0.61)
Month 18	2.86 (1.67, 4.05)	1.76 (-0.33, 3.85)	1.10 (-1.23, 3.42), 0.3535	0.21 (-0.54, 0.97)
p-value of Treatment*FAP Stage	0.6130			

Norfolk QoL-DN score = composite of 35 quality of life questions; lower scores indicate higher quality of life (range = -4 to 136). Nonmissing scores for items 27-33 imputed for patients who reported an impact due to COVID-19 pandemic. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.
LS estimates and p-value derived from mixed-effects model for repeated measures (MMRM), controlling for categorical factors (treatment, visit), the subgroup variable, continuous covariate (baseline value), and interaction (treatment by visit, treatment by subgroup).
Standardized effect size (d) = LS mean difference/estimated pooled standard deviation with the small sample bias correction.

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

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Table 3.5
Norfolk Quality of Life - Diabetic Neuropathy (QoL-DN) Domain Scores: Change from Baseline to Month 18, MMRM Model
Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A) Subgroup Analysis
mITT Population

Norfolk QoL-DN Domain: Activities of Daily Living (ADLs)

Subgroup Visit	LS Mean (95% CI) Vutrisiran (HELIOS-A) (N=122)	LS Mean (95% CI) Patisiran (HELIOS-A) (N=42)	LS Mean Difference (Vutrisiran-Patisiran) (95% CI), p-value	Standardized Effect Size (95% CI)
Cardiac Subpopulation				
Yes	38	14		
Month 9	0.25 (-0.80, 1.29)	2.50 (0.79, 4.21)	-2.25 (-4.24, -0.27), 0.0262	-0.62 (-1.24, -0.01)
Month 18	0.80 (-0.33, 1.94)	1.66 (-0.21, 3.54)	-0.86 (-3.03, 1.31), 0.4362	-0.19 (-0.81, 0.44)
No	79	26		
Month 9	-0.11 (-0.84, 0.62)	-0.29 (-1.57, 0.98)	0.18 (-1.27, 1.64), 0.8017	0.06 (-0.38, 0.50)
Month 18	0.45 (-0.40, 1.30)	-1.13 (-2.61, 0.35)	1.58 (-0.11, 3.27), 0.0674	0.43 (-0.02, 0.88)
p-value of Treatment*Cardiac Subpopulation	0.0500			

Norfolk QoL-DN score = composite of 35 quality of life questions; lower scores indicate higher quality of life (range = -4 to 136). Nonmissing scores for items 27-33 imputed for patients who reported an impact due to COVID-19 pandemic. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.
LS estimates and p-value derived from mixed-effects model for repeated measures (MMRM), controlling for categorical factors (treatment, visit), the subgroup variable, continuous covariate (baseline value), and interaction (treatment by visit, treatment by subgroup).
Standardized effect size (d) = LS mean difference/estimated pooled standard deviation with the small sample bias correction.

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

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Table 3.5
Norfolk Quality of Life - Diabetic Neuropathy (QoL-DN) Domain Scores: Change from Baseline to Month 18, MMRM Model
Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A) Subgroup Analysis
mITT Population

Norfolk QoL-DN Domain: Activities of Daily Living (ADLs)

Subgroup Visit	LS Mean (95% CI) Vutrisiran (HELIOS-A) (N=122)	LS Mean (95% CI) Patisiran (HELIOS-A) (N=42)	LS Mean Difference (Vutrisiran-Patisiran) (95% CI), p-value	Standardized Effect Size (95% CI)
Weight (kg)				
<65	44	15		
Month 9	-0.13 (-1.11, 0.85)	0.01 (-1.66, 1.68)	-0.14 (-2.08, 1.80), 0.8871	-0.03 (-0.61, 0.54)
Month 18	0.42 (-0.65, 1.50)	-0.83 (-2.67, 1.01)	1.25 (-0.88, 3.39), 0.2491	0.30 (-0.28, 0.88)
≥65	73	25		
Month 9	0.09 (-0.67, 0.86)	1.13 (-0.17, 2.42)	-1.03 (-2.53, 0.47), 0.1767	-0.37 (-0.83, 0.08)
Month 18	0.65 (-0.24, 1.54)	0.29 (-1.23, 1.81)	0.36 (-1.40, 2.12), 0.6865	0.09 (-0.38, 0.56)
p-value of Treatment*Weight	0.4705			

Norfolk QoL-DN score = composite of 35 quality of life questions; lower scores indicate higher quality of life (range = -4 to 136). Nonmissing scores for items 27-33 imputed for patients who reported an impact due to COVID-19 pandemic. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.
LS estimates and p-value derived from mixed-effects model for repeated measures (MMRM), controlling for categorical factors (treatment, visit), the subgroup variable, continuous covariate (baseline value), and interaction (treatment by visit, treatment by subgroup).
Standardized effect size (d) = LS mean difference/estimated pooled standard deviation with the small sample bias correction.

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

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Table 3.8
Norfolk Quality of Life - Diabetic Neuropathy (QoL-DN) Domain Scores: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Norfolk QoL-DN Domain: Activities of Daily Living (ADLs)

Age (years): <65

Subgroup Visit	Vutrisiran (HELIOS-A) (N=76)	Patisiran (HELIOS-A) (N=31)
Baseline		
n	75	31
Mean (SD)	4.9 (5.1)	4.8 (5.5)
SE	0.6	1.0
Median	3.0	2.0
Min, Max	0, 18	0, 20
Month 9		
Actual Value		
n	74	30
Mean (SD)	5.2 (5.7)	5.1 (6.1)
SE	0.7	1.1
Median	2.0	1.5
Min, Max	0, 17	0, 20
Change from baseline		
n	73	30
Mean (SD)	0.5 (3.3)	0.6 (3.7)
SE	0.4	0.7
Median	0.0	0.0
Min, Max	-14, 11	-9, 9

Norfolk QoL-DN score = composite of 35 quality of life questions; lower scores indicate higher quality of life (range = -4 to 136). Nonmissing scores for items 27-33 imputed for patients who reported an impact due to COVID-19 pandemic. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 3.8
Norfolk Quality of Life - Diabetic Neuropathy (QoL-DN) Domain Scores: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Norfolk QoL-DN Domain: Activities of Daily Living (ADLs)

Age (years): <65

Subgroup Visit	Vutrisiran (HELIOS-A) (N=76)	Patisiran (HELIOS-A) (N=31)
Month 18		
Actual Value		
n	74	29
Mean (SD)	5.2 (6.0)	4.2 (5.7)
SE	0.7	1.1
Median	2.0	1.0
Min, Max	0, 20	0, 18
Change from baseline		
n	73	29
Mean (SD)	0.5 (4.0)	0.3 (3.6)
SE	0.5	0.7
Median	0.0	0.0
Min, Max	-15, 13	-10, 11

Norfolk QoL-DN score = composite of 35 quality of life questions; lower scores indicate higher quality of life (range = -4 to 136). Nonmissing scores for items 27-33 imputed for patients who reported an impact due to COVID-19 pandemic. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 3.8
Norfolk Quality of Life - Diabetic Neuropathy (QoL-DN) Domain Scores: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Norfolk QoL-DN Domain: Activities of Daily Living (ADLs)

Age (years): ≥65

Subgroup Visit	Vutrisiran (HELIOS-A) (N=46)	Patisiran (HELIOS-A) (N=11)
Baseline		
n	46	11
Mean (SD)	7.0 (6.3)	5.7 (6.1)
SE	0.9	1.8
Median	5.5	5.0
Min, Max	0, 20	0, 19
Month 9		
Actual Value		
n	42	10
Mean (SD)	5.7 (6.0)	7.3 (6.7)
SE	0.9	2.1
Median	3.0	6.0
Min, Max	0, 19	0, 18
Change from baseline		
n	42	10
Mean (SD)	-0.9 (3.1)	1.5 (2.9)
SE	0.5	0.9
Median	0.0	0.0
Min, Max	-11, 6	-1, 9

Norfolk QoL-DN score = composite of 35 quality of life questions; lower scores indicate higher quality of life (range = -4 to 136). Nonmissing scores for items 27-33 imputed for patients who reported an impact due to COVID-19 pandemic. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 3.8
Norfolk Quality of Life - Diabetic Neuropathy (QoL-DN) Domain Scores: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Norfolk QoL-DN Domain: Activities of Daily Living (ADLs)

Age (years): ≥65

Subgroup Visit	Vutrisiran (HELIOS-A) (N=46)	Patisiran (HELIOS-A) (N=11)
Month 18		
Actual Value		
n	40	9
Mean (SD)	7.3 (6.8)	5.6 (5.6)
SE	1.1	1.9
Median	5.0	4.0
Min, Max	0, 20	0, 14
Change from baseline		
n	40	9
Mean (SD)	0.8 (4.5)	-0.9 (4.9)
SE	0.7	1.6
Median	0.5	0.0
Min, Max	-7, 18	-8, 9

Norfolk QoL-DN score = composite of 35 quality of life questions; lower scores indicate higher quality of life (range = -4 to 136). Nonmissing scores for items 27-33 imputed for patients who reported an impact due to COVID-19 pandemic. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 3.8
Norfolk Quality of Life - Diabetic Neuropathy (QoL-DN) Domain Scores: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Norfolk QoL-DN Domain: Activities of Daily Living (ADLs)

Sex: Male

Subgroup Visit	Vutrisiran (HELIOS-A) (N=79)	Patisiran (HELIOS-A) (N=27)
Baseline		
n	78	27
Mean (SD)	6.1 (5.8)	5.0 (5.4)
SE	0.7	1.0
Median	4.0	4.0
Min, Max	0, 20	0, 20
Month 9		
Actual Value		
n	76	25
Mean (SD)	5.6 (5.9)	5.9 (6.1)
SE	0.7	1.2
Median	3.0	3.0
Min, Max	0, 19	0, 20
Change from baseline		
n	75	25
Mean (SD)	-0.3 (3.6)	1.2 (3.7)
SE	0.4	0.7
Median	0.0	0.0
Min, Max	-14, 10	-5, 9

Norfolk QoL-DN score = composite of 35 quality of life questions; lower scores indicate higher quality of life (range = -4 to 136). Nonmissing scores for items 27-33 imputed for patients who reported an impact due to COVID-19 pandemic. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 3.8
Norfolk Quality of Life - Diabetic Neuropathy (QoL-DN) Domain Scores: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Norfolk QoL-DN Domain: Activities of Daily Living (ADLs)

Sex: Male

Subgroup Visit	Vutrisiran (HELIOS-A) (N=79)	Patisiran (HELIOS-A) (N=27)
Month 18		
Actual Value		
n	74	23
Mean (SD)	6.2 (6.6)	5.2 (5.8)
SE	0.8	1.2
Median	3.5	2.0
Min, Max	0, 20	0, 18
Change from baseline		
n	73	23
Mean (SD)	0.6 (4.6)	1.0 (3.4)
SE	0.5	0.7
Median	0.0	1.0
Min, Max	-15, 18	-5, 11

Norfolk QoL-DN score = composite of 35 quality of life questions; lower scores indicate higher quality of life (range = -4 to 136). Nonmissing scores for items 27-33 imputed for patients who reported an impact due to COVID-19 pandemic. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 3.8
Norfolk Quality of Life - Diabetic Neuropathy (QoL-DN) Domain Scores: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Norfolk QoL-DN Domain: Activities of Daily Living (ADLs)

Sex: Female

Subgroup Visit	Vutrisiran (HELIOS-A) (N=43)	Patisiran (HELIOS-A) (N=15)
Baseline		
n	43	15
Mean (SD)	5.1 (5.4)	5.1 (6.1)
SE	0.8	1.6
Median	3.0	1.0
Min, Max	0, 18	0, 19
Month 9		
Actual Value		
n	40	15
Mean (SD)	5.1 (5.7)	5.2 (6.7)
SE	0.9	1.7
Median	2.0	1.0
Min, Max	0, 17	0, 18
Change from baseline		
n	40	15
Mean (SD)	0.5 (2.5)	0.1 (3.2)
SE	0.4	0.8
Median	0.0	0.0
Min, Max	-4, 11	-9, 6

Norfolk QoL-DN score = composite of 35 quality of life questions; lower scores indicate higher quality of life (range = -4 to 136). Nonmissing scores for items 27-33 imputed for patients who reported an impact due to COVID-19 pandemic. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 3.8
Norfolk Quality of Life - Diabetic Neuropathy (QoL-DN) Domain Scores: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Norfolk QoL-DN Domain: Activities of Daily Living (ADLs)

Sex: Female

Subgroup Visit	Vutrisiran (HELIOS-A) (N=43)	Patisiran (HELIOS-A) (N=15)
Month 18		
Actual Value		
n	40	15
Mean (SD)	5.5 (5.8)	3.5 (5.4)
SE	0.9	1.4
Median	2.5	1.0
Min, Max	0, 17	0, 16
Change from baseline		
n	40	15
Mean (SD)	0.7 (3.4)	-1.6 (4.2)
SE	0.5	1.1
Median	0.0	0.0
Min, Max	-6, 9	-10, 4

Norfolk QoL-DN score = composite of 35 quality of life questions; lower scores indicate higher quality of life (range = -4 to 136). Nonmissing scores for items 27-33 imputed for patients who reported an impact due to COVID-19 pandemic. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 3.8
Norfolk Quality of Life - Diabetic Neuropathy (QoL-DN) Domain Scores: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Norfolk QoL-DN Domain: Activities of Daily Living (ADLs)

Race: White

Subgroup Visit	Vutrisiran (HELIOS-A) (N=86)	Patisiran (HELIOS-A) (N=29)
Baseline		
n	85	29
Mean (SD)	5.8 (5.9)	5.5 (5.8)
SE	0.6	1.1
Median	3.0	4.0
Min, Max	0, 20	0, 20
Month 9		
Actual Value		
n	82	28
Mean (SD)	5.7 (6.0)	6.1 (6.8)
SE	0.7	1.3
Median	3.0	3.0
Min, Max	0, 19	0, 20
Change from baseline		
n	81	28
Mean (SD)	0.2 (2.3)	0.6 (3.4)
SE	0.3	0.6
Median	0.0	0.0
Min, Max	-6, 6	-9, 9

Norfolk QoL-DN score = composite of 35 quality of life questions; lower scores indicate higher quality of life (range = -4 to 136). Nonmissing scores for items 27-33 imputed for patients who reported an impact due to COVID-19 pandemic. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Norfolk Quality of Life - Diabetic Neuropathy (QoL-DN) Domain Scores: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Norfolk QoL-DN Domain: Activities of Daily Living (ADLs)

Race: White

Subgroup Visit	Vutrisiran (HELIOS-A) (N=86)	Patisiran (HELIOS-A) (N=29)
Month 18		
Actual Value		
n	81	27
Mean (SD)	5.9 (6.4)	4.5 (5.8)
SE	0.7	1.1
Median	4.0	1.0
Min, Max	0, 20	0, 18
Change from baseline		
n	80	27
Mean (SD)	0.5 (3.3)	-0.4 (4.2)
SE	0.4	0.8
Median	0.0	0.0
Min, Max	-6, 10	-10, 11

Norfolk QoL-DN score = composite of 35 quality of life questions; lower scores indicate higher quality of life (range = -4 to 136). Nonmissing scores for items 27-33 imputed for patients who reported an impact due to COVID-19 pandemic. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 3.8
Norfolk Quality of Life - Diabetic Neuropathy (QoL-DN) Domain Scores: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Norfolk QoL-DN Domain: Activities of Daily Living (ADLs)

Race: All Other Races

Subgroup Visit	Vutrisiran (HELIOS-A) (N=36)	Patisiran (HELIOS-A) (N=13)
Baseline		
n	36	13
Mean (SD)	5.4 (5.1)	4.1 (5.2)
SE	0.9	1.4
Median	4.0	0.0
Min, Max	0, 18	0, 14
Month 9		
Actual Value		
n	34	12
Mean (SD)	4.8 (5.3)	4.4 (5.0)
SE	0.9	1.4
Median	2.5	2.0
Min, Max	0, 17	0, 14
Change from baseline		
n	34	12
Mean (SD)	-0.5 (5.0)	1.2 (3.9)
SE	0.8	1.1
Median	0.0	0.0
Min, Max	-14, 11	-3, 9

Norfolk QoL-DN score = composite of 35 quality of life questions; lower scores indicate higher quality of life (range = -4 to 136). Nonmissing scores for items 27-33 imputed for patients who reported an impact due to COVID-19 pandemic. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 3.8
Norfolk Quality of Life - Diabetic Neuropathy (QoL-DN) Domain Scores: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Norfolk QoL-DN Domain: Activities of Daily Living (ADLs)

Race: All Other Races

Subgroup Visit	Vutrisiran (HELIOS-A) (N=36)	Patisiran (HELIOS-A) (N=13)
Month 18		
Actual Value		
n	33	11
Mean (SD)	6.0 (6.3)	4.6 (5.4)
SE	1.1	1.6
Median	3.0	2.0
Min, Max	0, 20	0, 14
Change from baseline		
n	33	11
Mean (SD)	0.9 (5.9)	1.1 (2.9)
SE	1.0	0.9
Median	1.0	1.0
Min, Max	-15, 18	-2, 9

Norfolk QoL-DN score = composite of 35 quality of life questions; lower scores indicate higher quality of life (range = -4 to 136). Nonmissing scores for items 27-33 imputed for patients who reported an impact due to COVID-19 pandemic. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 3.8
Norfolk Quality of Life - Diabetic Neuropathy (QoL-DN) Domain Scores: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Norfolk QoL-DN Domain: Activities of Daily Living (ADLs)

Region: North America

Subgroup Visit	Vutrisiran (HELIOS-A) (N=27)	Patisiran (HELIOS-A) (N=8)
Baseline		
n	26	8
Mean (SD)	3.4 (3.9)	4.0 (4.1)
SE	0.8	1.5
Median	3.0	3.0
Min, Max	0, 15	0, 10
Month 9		
Actual Value		
n	25	8
Mean (SD)	2.7 (3.7)	5.0 (5.7)
SE	0.7	2.0
Median	1.0	2.0
Min, Max	0, 14	0, 14
Change from baseline		
n	24	8
Mean (SD)	-0.4 (3.6)	1.0 (3.8)
SE	0.7	1.3
Median	0.0	0.0
Min, Max	-14, 6	-4, 9

Norfolk QoL-DN score = composite of 35 quality of life questions; lower scores indicate higher quality of life (range = -4 to 136). Nonmissing scores for items 27-33 imputed for patients who reported an impact due to COVID-19 pandemic. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 3.8
Norfolk Quality of Life - Diabetic Neuropathy (QoL-DN) Domain Scores: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Norfolk QoL-DN Domain: Activities of Daily Living (ADLs)

Region: North America

Subgroup Visit	Vutrisiran (HELIOS-A) (N=27)	Patisiran (HELIOS-A) (N=8)
Month 18		
Actual Value		
n	25	7
Mean (SD)	3.2 (4.8)	4.6 (6.2)
SE	1.0	2.3
Median	1.0	1.0
Min, Max	0, 18	0, 14
Change from baseline		
n	24	7
Mean (SD)	-0.1 (5.3)	0.0 (5.7)
SE	1.1	2.1
Median	-0.5	0.0
Min, Max	-15, 18	-10, 9

Norfolk QoL-DN score = composite of 35 quality of life questions; lower scores indicate higher quality of life (range = -4 to 136). Nonmissing scores for items 27-33 imputed for patients who reported an impact due to COVID-19 pandemic. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

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Table 3.8
Norfolk Quality of Life - Diabetic Neuropathy (QoL-DN) Domain Scores: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Norfolk QoL-DN Domain: Activities of Daily Living (ADLs)

Region: Western Europe

Subgroup Visit	Vutrisiran (HELIOS-A) (N=42)	Patisiran (HELIOS-A) (N=20)
Baseline		
n	42	20
Mean (SD)	5.9 (6.2)	5.1 (5.6)
SE	1.0	1.3
Median	3.5	3.5
Min, Max	0, 19	0, 19
Month 9		
Actual Value		
n	39	18
Mean (SD)	5.6 (6.2)	4.4 (5.5)
SE	1.0	1.3
Median	2.0	2.5
Min, Max	0, 17	0, 18
Change from baseline		
n	39	18
Mean (SD)	0.2 (2.8)	-0.2 (3.1)
SE	0.5	0.7
Median	0.0	0.0
Min, Max	-6, 11	-9, 5

Norfolk QoL-DN score = composite of 35 quality of life questions; lower scores indicate higher quality of life (range = -4 to 136). Nonmissing scores for items 27-33 imputed for patients who reported an impact due to COVID-19 pandemic. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 3.8
Norfolk Quality of Life - Diabetic Neuropathy (QoL-DN) Domain Scores: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Norfolk QoL-DN Domain: Activities of Daily Living (ADLs)

Region: Western Europe

Subgroup Visit	Vutrisiran (HELIOS-A) (N=42)	Patisiran (HELIOS-A) (N=20)
Month 18		
Actual Value		
n	39	18
Mean (SD)	5.7 (6.1)	3.3 (4.0)
SE	1.0	0.9
Median	3.0	1.0
Min, Max	0, 18	0, 13
Change from baseline		
n	39	18
Mean (SD)	0.3 (3.1)	-1.3 (3.2)
SE	0.5	0.8
Median	0.0	0.0
Min, Max	-6, 8	-8, 4

Norfolk QoL-DN score = composite of 35 quality of life questions; lower scores indicate higher quality of life (range = -4 to 136). Nonmissing scores for items 27-33 imputed for patients who reported an impact due to COVID-19 pandemic. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 3.8
Norfolk Quality of Life - Diabetic Neuropathy (QoL-DN) Domain Scores: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Norfolk QoL-DN Domain: Activities of Daily Living (ADLs)

Region: Rest of World

Subgroup Visit	Vutrisiran (HELIOS-A) (N=53)	Patisiran (HELIOS-A) (N=14)
Baseline		
n	53	14
Mean (SD)	6.7 (5.8)	5.6 (6.5)
SE	0.8	1.8
Median	6.0	3.0
Min, Max	0, 20	0, 20
Month 9		
Actual Value		
n	52	14
Mean (SD)	6.6 (6.0)	7.5 (7.4)
SE	0.8	2.0
Median	6.0	7.0
Min, Max	0, 19	0, 20
Change from baseline		
n	52	14
Mean (SD)	0.0 (3.6)	1.9 (3.6)
SE	0.5	1.0
Median	0.0	0.0
Min, Max	-11, 10	-3, 9

Norfolk QoL-DN score = composite of 35 quality of life questions; lower scores indicate higher quality of life (range = -4 to 136). Nonmissing scores for items 27-33 imputed for patients who reported an impact due to COVID-19 pandemic. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 3.8
Norfolk Quality of Life - Diabetic Neuropathy (QoL-DN) Domain Scores: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Norfolk QoL-DN Domain: Activities of Daily Living (ADLs)

Region: Rest of World

Subgroup Visit	Vutrisiran (HELIOS-A) (N=53)	Patisiran (HELIOS-A) (N=14)
Month 18		
Actual Value		
n	50	13
Mean (SD)	7.6 (6.7)	6.3 (7.1)
SE	1.0	2.0
Median	6.0	2.0
Min, Max	0, 20	0, 18
Change from baseline		
n	50	13
Mean (SD)	1.2 (4.3)	1.8 (3.2)
SE	0.6	0.9
Median	0.5	1.0
Min, Max	-7, 13	-2, 11

Norfolk QoL-DN score = composite of 35 quality of life questions; lower scores indicate higher quality of life (range = -4 to 136). Nonmissing scores for items 27-33 imputed for patients who reported an impact due to COVID-19 pandemic. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 3.8
Norfolk Quality of Life - Diabetic Neuropathy (QoL-DN) Domain Scores: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Norfolk QoL-DN Domain: Activities of Daily Living (ADLs)

Baseline NIS: <50

Subgroup Visit	Vutrisiran (HELIOS-A) (N=78)	Patisiran (HELIOS-A) (N=27)
Baseline		
n	77	27
Mean (SD)	2.9 (3.6)	2.3 (3.6)
SE	0.4	0.7
Median	1.0	0.0
Min, Max	0, 15	0, 11
Month 9		
Actual Value		
n	77	27
Mean (SD)	2.4 (3.4)	3.0 (4.1)
SE	0.4	0.8
Median	1.0	1.0
Min, Max	0, 16	0, 14
Change from baseline		
n	76	27
Mean (SD)	-0.3 (2.8)	0.6 (3.5)
SE	0.3	0.7
Median	0.0	0.0
Min, Max	-14, 6	-9, 9

Norfolk QoL-DN score = composite of 35 quality of life questions; lower scores indicate higher quality of life (range = -4 to 136). Nonmissing scores for items 27-33 imputed for patients who reported an impact due to COVID-19 pandemic. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 3.8
Norfolk Quality of Life - Diabetic Neuropathy (QoL-DN) Domain Scores: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Norfolk QoL-DN Domain: Activities of Daily Living (ADLs)

Baseline NIS: <50

Subgroup Visit	Vutrisiran (HELIOS-A) (N=78)	Patisiran (HELIOS-A) (N=27)
Month 18		
Actual Value		
n	75	26
Mean (SD)	2.6 (4.0)	2.3 (4.2)
SE	0.5	0.8
Median	1.0	1.0
Min, Max	0, 18	0, 14
Change from baseline		
n	74	26
Mean (SD)	-0.1 (4.0)	-0.1 (3.5)
SE	0.5	0.7
Median	0.0	0.0
Min, Max	-15, 18	-10, 9

Norfolk QoL-DN score = composite of 35 quality of life questions; lower scores indicate higher quality of life (range = -4 to 136). Nonmissing scores for items 27-33 imputed for patients who reported an impact due to COVID-19 pandemic. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 3.8
Norfolk Quality of Life - Diabetic Neuropathy (QoL-DN) Domain Scores: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Norfolk QoL-DN Domain: Activities of Daily Living (ADLs)

Baseline NIS: ≥50

Subgroup Visit	Vutrisiran (HELIOS-A) (N=44)	Patisiran (HELIOS-A) (N=15)
Baseline		
n	44	15
Mean (SD)	10.6 (5.3)	9.9 (5.2)
SE	0.8	1.4
Median	11.0	10.0
Min, Max	1, 20	0, 20
Month 9		
Actual Value		
n	39	13
Mean (SD)	11.3 (5.0)	11.2 (6.5)
SE	0.8	1.8
Median	12.0	12.0
Min, Max	0, 19	1, 20
Change from baseline		
n	39	13
Mean (SD)	0.6 (4.1)	1.2 (3.6)
SE	0.7	1.0
Median	0.0	0.0
Min, Max	-10, 11	-5, 9

Norfolk QoL-DN score = composite of 35 quality of life questions; lower scores indicate higher quality of life (range = -4 to 136). Nonmissing scores for items 27-33 imputed for patients who reported an impact due to COVID-19 pandemic. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 3.8
Norfolk Quality of Life - Diabetic Neuropathy (QoL-DN) Domain Scores: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Norfolk QoL-DN Domain: Activities of Daily Living (ADLs)

Baseline NIS: ≥50

Subgroup Visit	Vutrisiran (HELIOS-A) (N=44)	Patisiran (HELIOS-A) (N=15)
Month 18		
Actual Value		
n	39	12
Mean (SD)	12.3 (5.0)	9.3 (5.4)
SE	0.8	1.5
Median	13.0	9.0
Min, Max	2, 20	2, 18
Change from baseline		
n	39	12
Mean (SD)	2.0 (4.3)	0.2 (4.9)
SE	0.7	1.4
Median	1.0	-0.5
Min, Max	-6, 13	-8, 11

Norfolk QoL-DN score = composite of 35 quality of life questions; lower scores indicate higher quality of life (range = -4 to 136). Nonmissing scores for items 27-33 imputed for patients who reported an impact due to COVID-19 pandemic. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 3.8
Norfolk Quality of Life - Diabetic Neuropathy (QoL-DN) Domain Scores: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Norfolk QoL-DN Domain: Activities of Daily Living (ADLs)

Previous Tetramer Stabilizer Use: Yes

Subgroup Visit	Vutrisiran (HELIOS-A) (N=75)	Patisiran (HELIOS-A) (N=33)
Baseline		
n	75	33
Mean (SD)	5.5 (5.6)	5.6 (6.0)
SE	0.6	1.0
Median	3.0	6.0
Min, Max	0, 18	0, 20
Month 9		
Actual Value		
n	74	32
Mean (SD)	5.4 (5.8)	5.9 (6.4)
SE	0.7	1.1
Median	3.0	3.0
Min, Max	0, 17	0, 20
Change from baseline		
n	74	32
Mean (SD)	0.1 (3.2)	0.6 (3.2)
SE	0.4	0.6
Median	0.0	0.0
Min, Max	-11, 10	-9, 9

Norfolk QoL-DN score = composite of 35 quality of life questions; lower scores indicate higher quality of life (range = -4 to 136). Nonmissing scores for items 27-33 imputed for patients who reported an impact due to COVID-19 pandemic. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 3.8
Norfolk Quality of Life - Diabetic Neuropathy (QoL-DN) Domain Scores: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Norfolk QoL-DN Domain: Activities of Daily Living (ADLs)

Previous Tetramer Stabilizer Use: Yes

Subgroup Visit	Vutrisiran (HELIOS-A) (N=75)	Patisiran (HELIOS-A) (N=33)
Month 18		
Actual Value		
n	71	31
Mean (SD)	6.1 (6.7)	4.5 (5.6)
SE	0.8	1.0
Median	3.0	1.0
Min, Max	0, 20	0, 18
Change from baseline		
n	71	31
Mean (SD)	0.9 (3.9)	-0.4 (4.0)
SE	0.5	0.7
Median	0.0	0.0
Min, Max	-7, 13	-10, 11

Norfolk QoL-DN score = composite of 35 quality of life questions; lower scores indicate higher quality of life (range = -4 to 136). Nonmissing scores for items 27-33 imputed for patients who reported an impact due to COVID-19 pandemic. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 3.8
Norfolk Quality of Life - Diabetic Neuropathy (QoL-DN) Domain Scores: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Norfolk QoL-DN Domain: Activities of Daily Living (ADLs)

Previous Tetramer Stabilizer Use: No

Subgroup Visit	Vutrisiran (HELIOS-A) (N=47)	Patisiran (HELIOS-A) (N=9)
Baseline		
n	46	9
Mean (SD)	6.1 (5.8)	2.9 (3.4)
SE	0.9	1.1
Median	4.0	2.0
Min, Max	0, 20	0, 10
Month 9		
Actual Value		
n	42	8
Mean (SD)	5.4 (5.9)	4.4 (5.9)
SE	0.9	2.1
Median	3.0	0.5
Min, Max	0, 19	0, 14
Change from baseline		
n	41	8
Mean (SD)	-0.2 (3.6)	1.8 (4.7)
SE	0.6	1.7
Median	0.0	0.0
Min, Max	-14, 11	-4, 9

Norfolk QoL-DN score = composite of 35 quality of life questions; lower scores indicate higher quality of life (range = -4 to 136). Nonmissing scores for items 27-33 imputed for patients who reported an impact due to COVID-19 pandemic. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 3.8
Norfolk Quality of Life - Diabetic Neuropathy (QoL-DN) Domain Scores: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Norfolk QoL-DN Domain: Activities of Daily Living (ADLs)

Previous Tetramer Stabilizer Use: No

Subgroup Visit	Vutrisiran (HELIOS-A) (N=47)	Patisiran (HELIOS-A) (N=9)
Month 18		
Actual Value		
n	43	7
Mean (SD)	5.7 (5.9)	4.6 (6.2)
SE	0.9	2.3
Median	4.0	1.0
Min, Max	0, 20	0, 14
Change from baseline		
n	42	7
Mean (SD)	0.0 (4.7)	1.6 (3.6)
SE	0.7	1.3
Median	0.0	0.0
Min, Max	-15, 18	-1, 9

Norfolk QoL-DN score = composite of 35 quality of life questions; lower scores indicate higher quality of life (range = -4 to 136). Nonmissing scores for items 27-33 imputed for patients who reported an impact due to COVID-19 pandemic. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 3.8
Norfolk Quality of Life - Diabetic Neuropathy (QoL-DN) Domain Scores: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Norfolk QoL-DN Domain: Activities of Daily Living (ADLs)

Genotype: V30M

Subgroup Visit	Vutrisiran (HELIOS-A) (N=54)	Patisiran (HELIOS-A) (N=20)
Baseline		
n	53	20
Mean (SD)	6.2 (6.3)	4.5 (5.4)
SE	0.9	1.2
Median	5.0	2.0
Min, Max	0, 20	0, 19
Month 9		
Actual Value		
n	52	20
Mean (SD)	5.3 (5.9)	4.7 (5.5)
SE	0.8	1.2
Median	3.0	2.5
Min, Max	0, 19	0, 18
Change from baseline		
n	51	20
Mean (SD)	-0.6 (3.2)	0.2 (2.0)
SE	0.4	0.5
Median	0.0	0.0
Min, Max	-14, 6	-5, 5

Norfolk QoL-DN score = composite of 35 quality of life questions; lower scores indicate higher quality of life (range = -4 to 136). Nonmissing scores for items 27-33 imputed for patients who reported an impact due to COVID-19 pandemic. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 3.8
Norfolk Quality of Life - Diabetic Neuropathy (QoL-DN) Domain Scores: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Norfolk QoL-DN Domain: Activities of Daily Living (ADLs)

Genotype: V30M

Subgroup Visit	Vutrisiran (HELIOS-A) (N=54)	Patisiran (HELIOS-A) (N=20)
Month 18		
Actual Value		
n	52	20
Mean (SD)	5.6 (6.4)	3.7 (4.4)
SE	0.9	1.0
Median	2.5	1.5
Min, Max	0, 20	0, 13
Change from baseline		
n	51	20
Mean (SD)	-0.1 (3.9)	-0.8 (2.7)
SE	0.5	0.6
Median	0.0	0.0
Min, Max	-15, 9	-8, 4

Norfolk QoL-DN score = composite of 35 quality of life questions; lower scores indicate higher quality of life (range = -4 to 136). Nonmissing scores for items 27-33 imputed for patients who reported an impact due to COVID-19 pandemic. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 3.8
Norfolk Quality of Life - Diabetic Neuropathy (QoL-DN) Domain Scores: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Norfolk QoL-DN Domain: Activities of Daily Living (ADLs)

Genotype: non-V30M

Subgroup Visit	Vutrisiran (HELIOS-A) (N=68)	Patisiran (HELIOS-A) (N=22)
Baseline		
n	68	22
Mean (SD)	5.4 (5.2)	5.5 (5.9)
SE	0.6	1.3
Median	3.0	4.5
Min, Max	0, 19	0, 20
Month 9		
Actual Value		
n	64	20
Mean (SD)	5.5 (5.8)	6.6 (7.0)
SE	0.7	1.6
Median	3.0	3.0
Min, Max	0, 17	0, 20
Change from baseline		
n	64	20
Mean (SD)	0.5 (3.3)	1.4 (4.5)
SE	0.4	1.0
Median	0.0	0.0
Min, Max	-11, 11	-9, 9

Norfolk QoL-DN score = composite of 35 quality of life questions; lower scores indicate higher quality of life (range = -4 to 136). Nonmissing scores for items 27-33 imputed for patients who reported an impact due to COVID-19 pandemic. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 3.8
Norfolk Quality of Life - Diabetic Neuropathy (QoL-DN) Domain Scores: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Norfolk QoL-DN Domain: Activities of Daily Living (ADLs)

Genotype: non-V30M

Subgroup Visit	Vutrisiran (HELIOS-A) (N=68)	Patisiran (HELIOS-A) (N=22)
Month 18		
Actual Value		
n	62	18
Mean (SD)	6.2 (6.3)	5.5 (6.7)
SE	0.8	1.6
Median	3.5	1.0
Min, Max	0, 20	0, 18
Change from baseline		
n	62	18
Mean (SD)	1.1 (4.4)	0.9 (4.8)
SE	0.6	1.1
Median	0.0	1.0
Min, Max	-6, 18	-10, 11

Norfolk QoL-DN score = composite of 35 quality of life questions; lower scores indicate higher quality of life (range = -4 to 136). Nonmissing scores for items 27-33 imputed for patients who reported an impact due to COVID-19 pandemic. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 3.8
Norfolk Quality of Life - Diabetic Neuropathy (QoL-DN) Domain Scores: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Norfolk QoL-DN Domain: Activities of Daily Living (ADLs)

FAP Stage: I

Subgroup Visit	Vutrisiran (HELIOS-A) (N=84)	Patisiran (HELIOS-A) (N=31)
Baseline		
n	83	31
Mean (SD)	3.7 (4.4)	3.3 (4.3)
SE	0.5	0.8
Median	2.0	1.0
Min, Max	0, 18	0, 12
Month 9		
Actual Value		
n	82	30
Mean (SD)	3.1 (4.1)	3.8 (4.9)
SE	0.5	0.9
Median	1.0	1.0
Min, Max	0, 16	0, 18
Change from baseline		
n	81	30
Mean (SD)	-0.4 (3.2)	0.6 (3.1)
SE	0.4	0.6
Median	0.0	0.0
Min, Max	-14, 11	-9, 9

Norfolk QoL-DN score = composite of 35 quality of life questions; lower scores indicate higher quality of life (range = -4 to 136). Nonmissing scores for items 27-33 imputed for patients who reported an impact due to COVID-19 pandemic. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 3.8
Norfolk Quality of Life - Diabetic Neuropathy (QoL-DN) Domain Scores: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Norfolk QoL-DN Domain: Activities of Daily Living (ADLs)

FAP Stage: I

Subgroup Visit	Vutrisiran (HELIOS-A) (N=84)	Patisiran (HELIOS-A) (N=31)
Month 18		
Actual Value		
n	81	30
Mean (SD)	3.3 (4.5)	3.0 (4.6)
SE	0.5	0.8
Median	1.0	1.0
Min, Max	0, 17	0, 16
Change from baseline		
n	80	30
Mean (SD)	0.0 (3.4)	-0.3 (3.0)
SE	0.4	0.5
Median	0.0	0.0
Min, Max	-15, 10	-10, 4

Norfolk QoL-DN score = composite of 35 quality of life questions; lower scores indicate higher quality of life (range = -4 to 136). Nonmissing scores for items 27-33 imputed for patients who reported an impact due to COVID-19 pandemic. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 3.8
Norfolk Quality of Life - Diabetic Neuropathy (QoL-DN) Domain Scores: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Norfolk QoL-DN Domain: Activities of Daily Living (ADLs)

FAP Stage: II&III

Subgroup Visit	Vutrisiran (HELIOS-A) (N=38)	Patisiran (HELIOS-A) (N=11)
Baseline		
n	38	11
Mean (SD)	10.2 (5.6)	10.0 (6.0)
SE	0.9	1.8
Median	10.0	10.0
Min, Max	0, 20	0, 20
Month 9		
Actual Value		
n	34	10
Mean (SD)	11.0 (5.6)	11.1 (7.0)
SE	1.0	2.2
Median	13.0	13.0
Min, Max	0, 19	0, 20
Change from baseline		
n	34	10
Mean (SD)	0.9 (3.5)	1.5 (4.6)
SE	0.6	1.5
Median	0.5	0.0
Min, Max	-6, 10	-5, 9

Norfolk QoL-DN score = composite of 35 quality of life questions; lower scores indicate higher quality of life (range = -4 to 136). Nonmissing scores for items 27-33 imputed for patients who reported an impact due to COVID-19 pandemic. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

Alnylam Pharmaceuticals Inc.
ALN-TTRSC02-002

Table 3.8
Norfolk Quality of Life - Diabetic Neuropathy (QoL-DN) Domain Scores: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Norfolk QoL-DN Domain: Activities of Daily Living (ADLs)

FAP Stage: II&III

Subgroup Visit	Vutrisiran (HELIOS-A) (N=38)	Patisiran (HELIOS-A) (N=11)
Month 18		
Actual Value		
n	33	8
Mean (SD)	12.4 (5.7)	10.5 (5.1)
SE	1.0	1.8
Median	14.0	11.0
Min, Max	1, 20	4, 18
Change from baseline		
n	33	8
Mean (SD)	2.2 (5.4)	1.0 (6.6)
SE	0.9	2.3
Median	1.0	-0.5
Min, Max	-7, 18	-8, 11

Norfolk QoL-DN score = composite of 35 quality of life questions; lower scores indicate higher quality of life (range = -4 to 136). Nonmissing scores for items 27-33 imputed for patients who reported an impact due to COVID-19 pandemic. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 3.8
Norfolk Quality of Life - Diabetic Neuropathy (QoL-DN) Domain Scores: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Norfolk QoL-DN Domain: Activities of Daily Living (ADLs)

Cardiac Subpopulation: Yes

Subgroup Visit	Vutrisiran (HELIOS-A) (N=40)	Patisiran (HELIOS-A) (N=14)
Baseline		
n	40	14
Mean (SD)	7.6 (6.1)	8.1 (6.8)
SE	1.0	1.8
Median	7.0	9.0
Min, Max	0, 20	0, 20
Month 9		
Actual Value		
n	38	14
Mean (SD)	7.4 (6.5)	10.1 (7.4)
SE	1.0	2.0
Median	6.5	12.5
Min, Max	0, 19	0, 20
Change from baseline		
n	38	14
Mean (SD)	-0.2 (3.7)	2.0 (3.7)
SE	0.6	1.0
Median	0.0	0.5
Min, Max	-11, 10	-3, 9

Norfolk QoL-DN score = composite of 35 quality of life questions; lower scores indicate higher quality of life (range = -4 to 136). Nonmissing scores for items 27-33 imputed for patients who reported an impact due to COVID-19 pandemic. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 3.8
Norfolk Quality of Life - Diabetic Neuropathy (QoL-DN) Domain Scores: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Norfolk QoL-DN Domain: Activities of Daily Living (ADLs)

Cardiac Subpopulation: Yes

Subgroup Visit	Vutrisiran (HELIOS-A) (N=40)	Patisiran (HELIOS-A) (N=14)
Month 18		
Actual Value		
n	37	13
Mean (SD)	8.2 (7.4)	8.9 (6.8)
SE	1.2	1.9
Median	5.0	11.0
Min, Max	0, 20	0, 18
Change from baseline		
n	37	13
Mean (SD)	0.6 (4.5)	1.7 (5.0)
SE	0.7	1.4
Median	0.0	1.0
Min, Max	-7, 13	-8, 11

Norfolk QoL-DN score = composite of 35 quality of life questions; lower scores indicate higher quality of life (range = -4 to 136). Nonmissing scores for items 27-33 imputed for patients who reported an impact due to COVID-19 pandemic. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 3.8
Norfolk Quality of Life - Diabetic Neuropathy (QoL-DN) Domain Scores: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Norfolk QoL-DN Domain: Activities of Daily Living (ADLs)

Cardiac Subpopulation: No

Subgroup Visit	Vutrisiran (HELIOS-A) (N=82)	Patisiran (HELIOS-A) (N=28)
Baseline		
n	81	28
Mean (SD)	4.8 (5.2)	3.5 (4.3)
SE	0.6	0.8
Median	3.0	1.5
Min, Max	0, 18	0, 14
Month 9		
Actual Value		
n	78	26
Mean (SD)	4.5 (5.3)	3.2 (4.0)
SE	0.6	0.8
Median	2.0	1.0
Min, Max	0, 17	0, 12
Change from baseline		
n	77	26
Mean (SD)	0.1 (3.1)	0.2 (3.3)
SE	0.4	0.6
Median	0.0	0.0
Min, Max	-14, 11	-9, 9

Norfolk QoL-DN score = composite of 35 quality of life questions; lower scores indicate higher quality of life (range = -4 to 136). Nonmissing scores for items 27-33 imputed for patients who reported an impact due to COVID-19 pandemic. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 3.8
Norfolk Quality of Life - Diabetic Neuropathy (QoL-DN) Domain Scores: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Norfolk QoL-DN Domain: Activities of Daily Living (ADLs)

Cardiac Subpopulation: No

Subgroup Visit	Vutrisiran (HELIOS-A) (N=82)	Patisiran (HELIOS-A) (N=28)
Month 18		
Actual Value		
n	77	25
Mean (SD)	4.9 (5.5)	2.3 (3.1)
SE	0.6	0.6
Median	2.0	1.0
Min, Max	0, 18	0, 13
Change from baseline		
n	76	25
Mean (SD)	0.6 (4.1)	-0.9 (3.0)
SE	0.5	0.6
Median	0.0	0.0
Min, Max	-15, 18	-10, 4

Norfolk QoL-DN score = composite of 35 quality of life questions; lower scores indicate higher quality of life (range = -4 to 136). Nonmissing scores for items 27-33 imputed for patients who reported an impact due to COVID-19 pandemic. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 3.8
Norfolk Quality of Life - Diabetic Neuropathy (QoL-DN) Domain Scores: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Norfolk QoL-DN Domain: Activities of Daily Living (ADLs)

Weight (kg): <65

Subgroup Visit	Vutrisiran (HELIOS-A) (N=46)	Patisiran (HELIOS-A) (N=15)
Baseline		
n	46	15
Mean (SD)	6.7 (5.8)	4.3 (5.9)
SE	0.9	1.5
Median	6.5	0.0
Min, Max	0, 19	0, 19
Month 9		
Actual Value		
n	44	15
Mean (SD)	6.3 (5.8)	4.5 (6.4)
SE	0.9	1.7
Median	3.5	1.0
Min, Max	0, 17	0, 18
Change from baseline		
n	44	15
Mean (SD)	-0.3 (4.2)	0.1 (4.2)
SE	0.6	1.1
Median	0.0	0.0
Min, Max	-14, 11	-9, 9

Norfolk QoL-DN score = composite of 35 quality of life questions; lower scores indicate higher quality of life (range = -4 to 136). Nonmissing scores for items 27-33 imputed for patients who reported an impact due to COVID-19 pandemic. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 3.8
Norfolk Quality of Life - Diabetic Neuropathy (QoL-DN) Domain Scores: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Norfolk QoL-DN Domain: Activities of Daily Living (ADLs)

Weight (kg): <65

Subgroup Visit	Vutrisiran (HELIOS-A) (N=46)	Patisiran (HELIOS-A) (N=15)
Month 18		
Actual Value		
n	42	15
Mean (SD)	6.9 (6.3)	3.8 (5.3)
SE	1.0	1.4
Median	5.5	1.0
Min, Max	0, 20	0, 16
Change from baseline		
n	42	15
Mean (SD)	0.6 (4.6)	-0.5 (3.4)
SE	0.7	0.9
Median	0.0	0.0
Min, Max	-15, 13	-8, 4

Norfolk QoL-DN score = composite of 35 quality of life questions; lower scores indicate higher quality of life (range = -4 to 136). Nonmissing scores for items 27-33 imputed for patients who reported an impact due to COVID-19 pandemic. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 3.8
Norfolk Quality of Life - Diabetic Neuropathy (QoL-DN) Domain Scores: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Norfolk QoL-DN Domain: Activities of Daily Living (ADLs)

Weight (kg): ≥65

Subgroup Visit	Vutrisiran (HELIOS-A) (N=76)	Patisiran (HELIOS-A) (N=27)
Baseline		
n	75	27
Mean (SD)	5.1 (5.5)	5.4 (5.5)
SE	0.6	1.1
Median	3.0	5.0
Min, Max	0, 20	0, 20
Month 9		
Actual Value		
n	72	25
Mean (SD)	4.9 (5.8)	6.3 (6.2)
SE	0.7	1.2
Median	2.0	6.0
Min, Max	0, 19	0, 20
Change from baseline		
n	71	25
Mean (SD)	0.2 (2.6)	1.2 (3.0)
SE	0.3	0.6
Median	0.0	0.0
Min, Max	-11, 6	-4, 9

Norfolk QoL-DN score = composite of 35 quality of life questions; lower scores indicate higher quality of life (range = -4 to 136). Nonmissing scores for items 27-33 imputed for patients who reported an impact due to COVID-19 pandemic. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

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Table 3.8
Norfolk Quality of Life - Diabetic Neuropathy (QoL-DN) Domain Scores: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Norfolk QoL-DN Domain: Activities of Daily Living (ADLs)

Weight (kg): ≥65

Subgroup Visit	Vutrisiran (HELIOS-A) (N=76)	Patisiran (HELIOS-A) (N=27)
Month 18		
Actual Value		
n	72	23
Mean (SD)	5.4 (6.3)	5.0 (5.9)
SE	0.7	1.2
Median	2.0	1.0
Min, Max	0, 20	0, 18
Change from baseline		
n	71	23
Mean (SD)	0.6 (4.0)	0.3 (4.3)
SE	0.5	0.9
Median	0.0	0.0
Min, Max	-6, 18	-10, 11

Norfolk QoL-DN score = composite of 35 quality of life questions; lower scores indicate higher quality of life (range = -4 to 136). Nonmissing scores for items 27-33 imputed for patients who reported an impact due to COVID-19 pandemic. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

Norfolk-QoL-DN – Domäne Symptome

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Table 3.5
Norfolk Quality of Life - Diabetic Neuropathy (QoL-DN) Domain Scores: Change from Baseline to Month 18, MMRM Model
Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A) Subgroup Analysis
mITT Population

Norfolk QoL-DN Domain: Symptoms

Subgroup Visit	LS Mean (95% CI) Vutrisiran (HELIOS-A) (N=122)	LS Mean (95% CI) Patisiran (HELIOS-A) (N=42)	LS Mean Difference (Vutrisiran-Patisiran) (95% CI), p-value	Standardized Effect Size (95% CI)
Age (years)				
<65	73	30		
Month 9	-0.71 (-1.70, 0.28)	-1.32 (-2.87, 0.23)	0.61 (-1.23, 2.45), 0.5130	0.14 (-0.28, 0.56)
Month 18	-0.51 (-1.59, 0.56)	-0.64 (-2.36, 1.07)	0.13 (-1.89, 2.15), 0.9002	0.03 (-0.40, 0.45)
≥65	43	10		
Month 9	-1.83 (-3.11, -0.56)	-0.54 (-3.14, 2.06)	-1.29 (-4.19, 1.60), 0.3789	-0.30 (-0.98, 0.38)
Month 18	-1.64 (-2.98, -0.29)	0.14 (-2.57, 2.85)	-1.78 (-4.80, 1.25), 0.2487	-0.35 (-1.07, 0.36)
p-value of Treatment*Age	0.2616			

Norfolk QoL-DN score = composite of 35 quality of life questions; lower scores indicate higher quality of life (range = -4 to 136). Nonmissing scores for items 27-33 imputed for patients who reported an impact due to COVID-19 pandemic. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.
LS estimates and p-value derived from mixed-effects model for repeated measures (MMRM), controlling for categorical factors (treatment, visit), the subgroup variable, continuous covariate (baseline value), and interaction (treatment by visit, treatment by subgroup).
Standardized effect size (d) = LS mean difference/estimated pooled standard deviation with the small sample bias correction.

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

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Table 3.5
Norfolk Quality of Life - Diabetic Neuropathy (QoL-DN) Domain Scores: Change from Baseline to Month 18, MMRM Model
Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A) Subgroup Analysis
mITT Population

Norfolk QoL-DN Domain: Symptoms

Subgroup Visit	LS Mean (95% CI) Vutrisiran (HELIOS-A) (N=122)	LS Mean (95% CI) Patisiran (HELIOS-A) (N=42)	LS Mean Difference (Vutrisiran-Patisiran) (95% CI), p-value	Standardized Effect Size (95% CI)
Sex				
Male	75	25		
Month 9	-0.83 (-1.81, 0.16)	-0.85 (-2.54, 0.85)	0.02 (-1.94, 1.98), 0.9843	0.00 (-0.45, 0.45)
Month 18	-0.63 (-1.69, 0.44)	-0.17 (-2.01, 1.68)	-0.46 (-2.59, 1.67), 0.6700	-0.09 (-0.56, 0.37)
Female	41	15		
Month 9	-1.67 (-2.97, -0.37)	-1.59 (-3.74, 0.56)	-0.08 (-2.59, 2.43), 0.9510	-0.02 (-0.60, 0.57)
Month 18	-1.47 (-2.82, -0.11)	-0.91 (-3.15, 1.33)	-0.56 (-3.18, 2.06), 0.6750	-0.12 (-0.70, 0.47)
p-value of Treatment*Sex	0.9498			

Norfolk QoL-DN score = composite of 35 quality of life questions; lower scores indicate higher quality of life (range = -4 to 136). Nonmissing scores for items 27-33 imputed for patients who reported an impact due to COVID-19 pandemic. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.
LS estimates and p-value derived from mixed-effects model for repeated measures (MMRM), controlling for categorical factors (treatment, visit), the subgroup variable, continuous covariate (baseline value), and interaction (treatment by visit, treatment by subgroup).
Standardized effect size (d) = LS mean difference/estimated pooled standard deviation with the small sample bias correction.

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Table 3.5
Norfolk Quality of Life - Diabetic Neuropathy (QoL-DN) Domain Scores: Change from Baseline to Month 18, MMRM Model
Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A) Subgroup Analysis
mITT Population

Norfolk QoL-DN Domain: Symptoms

Subgroup Visit	LS Mean (95% CI) Vutrisiran (HELIOS-A) (N=122)	LS Mean (95% CI) Patisiran (HELIOS-A) (N=42)	LS Mean Difference (Vutrisiran-Patisiran) (95% CI), p-value	Standardized Effect Size (95% CI)
Race				
White	81	28		
Month 9	-1.30 (-2.26, -0.35)	-1.09 (-2.71, 0.54)	-0.21 (-2.10, 1.67), 0.8239	-0.05 (-0.48, 0.38)
Month 18	-1.10 (-2.13, -0.07)	-0.41 (-2.17, 1.35)	-0.69 (-2.73, 1.35), 0.5061	-0.15 (-0.58, 0.29)
All Other Races	35	12		
Month 9	-0.72 (-2.13, 0.70)	-1.22 (-3.65, 1.21)	0.50 (-2.30, 3.31), 0.7233	0.12 (-0.53, 0.76)
Month 18	-0.51 (-1.98, 0.95)	-0.54 (-3.08, 1.99)	0.03 (-2.89, 2.95), 0.9848	0.01 (-0.66, 0.68)
p-value of Treatment*Race	0.6677			

Norfolk QoL-DN score = composite of 35 quality of life questions; lower scores indicate higher quality of life (range = -4 to 136). Nonmissing scores for items 27-33 imputed for patients who reported an impact due to COVID-19 pandemic. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.
LS estimates and p-value derived from mixed-effects model for repeated measures (MMRM), controlling for categorical factors (treatment, visit), the subgroup variable, continuous covariate (baseline value), and interaction (treatment by visit, treatment by subgroup).
Standardized effect size (d) = LS mean difference/estimated pooled standard deviation with the small sample bias correction.

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Table 3.5
Norfolk Quality of Life - Diabetic Neuropathy (QoL-DN) Domain Scores: Change from Baseline to Month 18, MMRM Model
Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A) Subgroup Analysis
mITT Population

Norfolk QoL-DN Domain: Symptoms

Subgroup Visit	LS Mean (95% CI) Vutrisiran (HELIOS-A) (N=122)	LS Mean (95% CI) Patisiran (HELIOS-A) (N=42)	LS Mean Difference (Vutrisiran-Patisiran) (95% CI), p-value	Standardized Effect Size (95% CI)
Region				
North America	26	8		
Month 9	-1.50 (-3.14, 0.15)	-2.09 (-5.02, 0.83)	0.60 (-2.76, 3.95), 0.7252	0.17 (-0.61, 0.95)
Month 18	-1.29 (-2.98, 0.40)	-1.43 (-4.46, 1.60)	0.14 (-3.33, 3.60), 0.9376	0.03 (-0.79, 0.85)
Western Europe	38	18		
Month 9	-1.55 (-2.90, -0.20)	-0.62 (-2.60, 1.37)	-0.93 (-3.34, 1.47), 0.4443	-0.21 (-0.77, 0.34)
Month 18	-1.34 (-2.76, 0.07)	0.05 (-2.05, 2.15)	-1.39 (-3.93, 1.14), 0.2788	-0.28 (-0.84, 0.27)
Rest of World	52	14		
Month 9	-0.64 (-1.81, 0.53)	-1.23 (-3.46, 1.00)	0.59 (-1.93, 3.11), 0.6432	0.12 (-0.46, 0.71)
Month 18	-0.43 (-1.67, 0.81)	-0.57 (-2.92, 1.78)	0.13 (-2.53, 2.79), 0.9224	0.03 (-0.58, 0.63)
p-value of Treatment*Region	0.6165			

Norfolk QoL-DN score = composite of 35 quality of life questions; lower scores indicate higher quality of life (range = -4 to 136). Nonmissing scores for items 27-33 imputed for patients who reported an impact due to COVID-19 pandemic. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.
LS estimates and p-value derived from mixed-effects model for repeated measures (MMRM), controlling for categorical factors (treatment, visit), the subgroup variable, continuous covariate (baseline value), and interaction (treatment by visit, treatment by subgroup).
Standardized effect size (d) = LS mean difference/estimated pooled standard deviation with the small sample bias correction.

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Table 3.5
Norfolk Quality of Life - Diabetic Neuropathy (QoL-DN) Domain Scores: Change from Baseline to Month 18, MMRM Model
Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A) Subgroup Analysis
mITT Population

Norfolk QoL-DN Domain: Symptoms

Subgroup Visit	LS Mean (95% CI) Vutrisiran (HELIOS-A) (N=122)	LS Mean (95% CI) Patisiran (HELIOS-A) (N=42)	LS Mean Difference (Vutrisiran-Patisiran) (95% CI), p-value	Standardized Effect Size (95% CI)
Baseline NIS				
<50	75	27		
Month 9	-2.15 (-3.08, -1.21)	-2.25 (-3.81, -0.68)	0.10 (-1.70, 1.90), 0.9136	0.03 (-0.41, 0.46)
Month 18	-1.95 (-3.00, -0.91)	-1.57 (-3.32, 0.19)	-0.39 (-2.41, 1.64), 0.7062	-0.08 (-0.53, 0.36)
≥50	41	13		
Month 9	0.76 (-0.50, 2.02)	1.21 (-1.02, 3.44)	-0.45 (-2.97, 2.07), 0.7243	-0.09 (-0.71, 0.53)
Month 18	0.95 (-0.38, 2.29)	1.89 (-0.49, 4.27)	-0.94 (-3.62, 1.75), 0.4920	-0.19 (-0.83, 0.45)
p-value of Treatment*Baseline NIS	0.7193			

Norfolk QoL-DN score = composite of 35 quality of life questions; lower scores indicate higher quality of life (range = -4 to 136). Nonmissing scores for items 27-33 imputed for patients who reported an impact due to COVID-19 pandemic. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.
LS estimates and p-value derived from mixed-effects model for repeated measures (MMRM), controlling for categorical factors (treatment, visit), the subgroup variable, continuous covariate (baseline value), and interaction (treatment by visit, treatment by subgroup).
Standardized effect size (d) = LS mean difference/estimated pooled standard deviation with the small sample bias correction.

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Table 3.5
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Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A) Subgroup Analysis
mITT Population

Norfolk QoL-DN Domain: Symptoms

Subgroup Visit	LS Mean (95% CI) Vutrisiran (HELIOS-A) (N=122)	LS Mean (95% CI) Patisiran (HELIOS-A) (N=42)	LS Mean Difference (Vutrisiran-Patisiran) (95% CI), p-value	Standardized Effect Size (95% CI)
Previous Tetramer Stabilizer Use				
Yes	74	32		
Month 9	-0.90 (-1.89, 0.08)	-0.84 (-2.36, 0.68)	-0.06 (-1.88, 1.75), 0.9449	-0.01 (-0.43, 0.40)
Month 18	-0.70 (-1.77, 0.37)	-0.17 (-1.85, 1.50)	-0.53 (-2.51, 1.46), 0.6020	-0.10 (-0.52, 0.31)
No	42	8		
Month 9	-1.52 (-2.82, -0.23)	-2.27 (-5.20, 0.66)	0.75 (-2.46, 3.95), 0.6471	0.19 (-0.55, 0.94)
Month 18	-1.32 (-2.67, 0.03)	-1.60 (-4.64, 1.43)	0.28 (-3.04, 3.61), 0.8669	0.06 (-0.73, 0.85)
p-value of Treatment*Previous Tetramer Stabilizer Use	0.6587			

Norfolk QoL-DN score = composite of 35 quality of life questions; lower scores indicate higher quality of life (range = -4 to 136). Nonmissing scores for items 27-33 imputed for patients who reported an impact due to COVID-19 pandemic. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.
LS estimates and p-value derived from mixed-effects model for repeated measures (MMRM), controlling for categorical factors (treatment, visit), the subgroup variable, continuous covariate (baseline value), and interaction (treatment by visit, treatment by subgroup).
Standardized effect size (d) = LS mean difference/estimated pooled standard deviation with the small sample bias correction.

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Table 3.5
Norfolk Quality of Life - Diabetic Neuropathy (QoL-DN) Domain Scores: Change from Baseline to Month 18, MMRM Model
Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A) Subgroup Analysis
mITT Population

Norfolk QoL-DN Domain: Symptoms

Subgroup Visit	LS Mean (95% CI) Vutrisiran (HELIOS-A) (N=122)	LS Mean (95% CI) Patisiran (HELIOS-A) (N=42)	LS Mean Difference (Vutrisiran-Patisiran) (95% CI), p-value	Standardized Effect Size (95% CI)
Genotype				
V30M	52	20		
Month 9	-1.72 (-2.89, -0.55)	-0.55 (-2.44, 1.33)	-1.17 (-3.39, 1.06), 0.3020	-0.26 (-0.78, 0.25)
Month 18	-1.52 (-2.74, -0.29)	0.11 (-1.87, 2.09)	-1.63 (-3.96, 0.71), 0.1708	-0.35 (-0.87, 0.16)
non-V30M	64	20		
Month 9	-0.65 (-1.70, 0.41)	-1.70 (-3.58, 0.18)	1.05 (-1.11, 3.22), 0.3381	0.24 (-0.26, 0.74)
Month 18	-0.44 (-1.57, 0.68)	-1.04 (-3.05, 0.98)	0.59 (-1.72, 2.91), 0.6132	0.12 (-0.40, 0.64)
p-value of Treatment*Genotype	0.1463			

Norfolk QoL-DN score = composite of 35 quality of life questions; lower scores indicate higher quality of life (range = -4 to 136). Nonmissing scores for items 27-33 imputed for patients who reported an impact due to COVID-19 pandemic. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.
LS estimates and p-value derived from mixed-effects model for repeated measures (MMRM), controlling for categorical factors (treatment, visit), the subgroup variable, continuous covariate (baseline value), and interaction (treatment by visit, treatment by subgroup).
Standardized effect size (d) = LS mean difference/estimated pooled standard deviation with the small sample bias correction.

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Table 3.5
Norfolk Quality of Life - Diabetic Neuropathy (QoL-DN) Domain Scores: Change from Baseline to Month 18, MMRM Model
Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A) Subgroup Analysis
mITT Population

Norfolk QoL-DN Domain: Symptoms

Subgroup Visit	LS Mean (95% CI) Vutrisiran (HELIOS-A) (N=122)	LS Mean (95% CI) Patisiran (HELIOS-A) (N=42)	LS Mean Difference (Vutrisiran-Patisiran) (95% CI), p-value	Standardized Effect Size (95% CI)
FAP Stage				
I	81	30		
Month 9	-1.57 (-2.50, -0.64)	-2.23 (-3.75, -0.70)	0.66 (-1.12, 2.43), 0.4663	0.17 (-0.25, 0.58)
Month 18	-1.37 (-2.38, -0.36)	-1.49 (-3.16, 0.18)	0.12 (-1.82, 2.06), 0.9020	0.03 (-0.39, 0.44)
II&III	35	10		
Month 9	-0.11 (-1.49, 1.27)	2.19 (-0.40, 4.78)	-2.30 (-5.19, 0.60), 0.1189	-0.46 (-1.16, 0.24)
Month 18	0.10 (-1.34, 1.54)	2.93 (0.21, 5.65)	-2.83 (-5.87, 0.21), 0.0676	-0.50 (-1.27, 0.26)
p-value of Treatment*FAP Stage	0.0794			

Norfolk QoL-DN score = composite of 35 quality of life questions; lower scores indicate higher quality of life (range = -4 to 136). Nonmissing scores for items 27-33 imputed for patients who reported an impact due to COVID-19 pandemic. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.
LS estimates and p-value derived from mixed-effects model for repeated measures (MMRM), controlling for categorical factors (treatment, visit), the subgroup variable, continuous covariate (baseline value), and interaction (treatment by visit, treatment by subgroup).
Standardized effect size (d) = LS mean difference/estimated pooled standard deviation with the small sample bias correction.

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Table 3.5
Norfolk Quality of Life - Diabetic Neuropathy (QoL-DN) Domain Scores: Change from Baseline to Month 18, MMRM Model
Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A) Subgroup Analysis
mITT Population

Norfolk QoL-DN Domain: Symptoms

Subgroup Visit	LS Mean (95% CI) Vutrisiran (HELIOS-A) (N=122)	LS Mean (95% CI) Patisiran (HELIOS-A) (N=42)	LS Mean Difference (Vutrisiran-Patisiran) (95% CI), p-value	Standardized Effect Size (95% CI)
Cardiac Subpopulation				
Yes	38	14		
Month 9	-1.66 (-3.00, -0.31)	-0.63 (-2.86, 1.61)	-1.03 (-3.63, 1.57), 0.4342	-0.21 (-0.82, 0.39)
Month 18	-1.46 (-2.87, -0.05)	0.05 (-2.30, 2.41)	-1.51 (-4.24, 1.22), 0.2767	-0.30 (-0.93, 0.32)
No	78	26		
Month 9	-0.86 (-1.83, 0.11)	-1.40 (-3.06, 0.27)	0.53 (-1.39, 2.46), 0.5840	0.13 (-0.31, 0.57)
Month 18	-0.66 (-1.71, 0.39)	-0.72 (-2.53, 1.10)	0.06 (-2.04, 2.15), 0.9587	0.01 (-0.44, 0.46)
p-value of Treatment*Cardiac Subpopulation	0.3247			

Norfolk QoL-DN score = composite of 35 quality of life questions; lower scores indicate higher quality of life (range = -4 to 136). Nonmissing scores for items 27-33 imputed for patients who reported an impact due to COVID-19 pandemic. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.
LS estimates and p-value derived from mixed-effects model for repeated measures (MMRM), controlling for categorical factors (treatment, visit), the subgroup variable, continuous covariate (baseline value), and interaction (treatment by visit, treatment by subgroup).
Standardized effect size (d) = LS mean difference/estimated pooled standard deviation with the small sample bias correction.

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Table 3.5
Norfolk Quality of Life - Diabetic Neuropathy (QoL-DN) Domain Scores: Change from Baseline to Month 18, MMRM Model
Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A) Subgroup Analysis
mITT Population

Norfolk QoL-DN Domain: Symptoms

Subgroup Visit	LS Mean (95% CI) Vutrisiran (HELIOS-A) (N=122)	LS Mean (95% CI) Patisiran (HELIOS-A) (N=42)	LS Mean Difference (Vutrisiran-Patisiran) (95% CI), p-value	Standardized Effect Size (95% CI)
Weight (kg)				
<65	44	15		
Month 9	-0.55 (-1.80, 0.71)	-1.51 (-3.66, 0.63)	0.97 (-1.52, 3.45), 0.4443	0.26 (-0.32, 0.84)
Month 18	-0.34 (-1.66, 0.98)	-0.83 (-3.07, 1.41)	0.49 (-2.11, 3.09), 0.7114	0.10 (-0.48, 0.69)
≥65	72	25		
Month 9	-1.48 (-2.49, -0.48)	-0.90 (-2.59, 0.80)	-0.59 (-2.56, 1.38), 0.5575	-0.12 (-0.58, 0.33)
Month 18	-1.28 (-2.35, -0.20)	-0.21 (-2.06, 1.63)	-1.06 (-3.20, 1.07), 0.3268	-0.21 (-0.68, 0.26)
p-value of Treatment*Weight	0.3175			

Norfolk QoL-DN score = composite of 35 quality of life questions; lower scores indicate higher quality of life (range = -4 to 136). Nonmissing scores for items 27-33 imputed for patients who reported an impact due to COVID-19 pandemic. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.
LS estimates and p-value derived from mixed-effects model for repeated measures (MMRM), controlling for categorical factors (treatment, visit), the subgroup variable, continuous covariate (baseline value), and interaction (treatment by visit, treatment by subgroup).
Standardized effect size (d) = LS mean difference/estimated pooled standard deviation with the small sample bias correction.

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Table 3.8
Norfolk Quality of Life - Diabetic Neuropathy (QoL-DN) Domain Scores: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Norfolk QoL-DN Domain: Symptoms

Age (years): <65

Subgroup Visit	Vutrisiran (HELIOS-A) (N=76)	Patisiran (HELIOS-A) (N=31)
Baseline		
n	74	31
Mean (SD)	11.4 (6.5)	11.3 (7.3)
SE	0.8	1.3
Median	10.0	12.0
Min, Max	0, 31	0, 31
Month 9		
Actual Value		
n	74	30
Mean (SD)	10.4 (7.1)	9.5 (6.2)
SE	0.8	1.1
Median	10.5	9.0
Min, Max	0, 31	1, 23
Change from baseline		
n	72	30
Mean (SD)	-0.8 (4.6)	-1.5 (4.7)
SE	0.5	0.9
Median	-0.5	-1.0
Min, Max	-12, 10	-14, 8

Norfolk QoL-DN score = composite of 35 quality of life questions; lower scores indicate higher quality of life (range = -4 to 136). Nonmissing scores for items 27-33 imputed for patients who reported an impact due to COVID-19 pandemic. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 3.8
Norfolk Quality of Life - Diabetic Neuropathy (QoL-DN) Domain Scores: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Norfolk QoL-DN Domain: Symptoms

Age (years): <65

Subgroup Visit	Vutrisiran (HELIOS-A) (N=76)	Patisiran (HELIOS-A) (N=31)
Month 18		
Actual Value		
n	74	29
Mean (SD)	10.5 (6.6)	10.3 (6.9)
SE	0.8	1.3
Median	11.0	9.0
Min, Max	0, 32	1, 24
Change from baseline		
n	72	29
Mean (SD)	-0.8 (5.2)	0.0 (5.2)
SE	0.6	1.0
Median	-0.5	0.0
Min, Max	-11, 14	-11, 10

Norfolk QoL-DN score = composite of 35 quality of life questions; lower scores indicate higher quality of life (range = -4 to 136). Nonmissing scores for items 27-33 imputed for patients who reported an impact due to COVID-19 pandemic. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 3.8
Norfolk Quality of Life - Diabetic Neuropathy (QoL-DN) Domain Scores: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Norfolk QoL-DN Domain: Symptoms

Age (years): ≥65

Subgroup Visit	Vutrisiran (HELIOS-A) (N=46)	Patisiran (HELIOS-A) (N=11)
Baseline		
n	46	11
Mean (SD)	10.3 (5.3)	10.9 (7.5)
SE	0.8	2.3
Median	10.0	8.0
Min, Max	2, 22	0, 21
Month 9		
Actual Value		
n	42	10
Mean (SD)	8.4 (4.3)	11.4 (9.9)
SE	0.7	3.1
Median	8.0	8.5
Min, Max	1, 20	0, 28
Change from baseline		
n	42	10
Mean (SD)	-1.7 (4.6)	0.0 (5.8)
SE	0.7	1.8
Median	-1.0	-0.5
Min, Max	-14, 7	-8, 11

Norfolk QoL-DN score = composite of 35 quality of life questions; lower scores indicate higher quality of life (range = -4 to 136). Nonmissing scores for items 27-33 imputed for patients who reported an impact due to COVID-19 pandemic. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 3.8
Norfolk Quality of Life - Diabetic Neuropathy (QoL-DN) Domain Scores: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Norfolk QoL-DN Domain: Symptoms

Age (years): ≥65

Subgroup Visit	Vutrisiran (HELIOS-A) (N=46)	Patisiran (HELIOS-A) (N=11)
Month 18		
Actual Value		
n	40	9
Mean (SD)	8.7 (4.7)	10.7 (7.7)
SE	0.7	2.6
Median	8.0	10.0
Min, Max	3, 20	3, 23
Change from baseline		
n	40	9
Mean (SD)	-1.0 (5.7)	-1.2 (6.0)
SE	0.9	2.0
Median	-0.5	0.0
Min, Max	-16, 13	-10, 6

Norfolk QoL-DN score = composite of 35 quality of life questions; lower scores indicate higher quality of life (range = -4 to 136). Nonmissing scores for items 27-33 imputed for patients who reported an impact due to COVID-19 pandemic. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 3.8
Norfolk Quality of Life - Diabetic Neuropathy (QoL-DN) Domain Scores: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Norfolk QoL-DN Domain: Symptoms

Sex: Male

Subgroup Visit	Vutrisiran (HELIOS-A) (N=79)	Patisiran (HELIOS-A) (N=27)
Baseline		
n	77	27
Mean (SD)	10.9 (6.2)	11.3 (7.2)
SE	0.7	1.4
Median	10.0	10.0
Min, Max	0, 31	0, 31
Month 9		
Actual Value		
n	76	25
Mean (SD)	9.8 (6.7)	10.2 (7.1)
SE	0.8	1.4
Median	9.0	10.0
Min, Max	0, 31	0, 28
Change from baseline		
n	74	25
Mean (SD)	-1.0 (4.7)	-0.9 (4.4)
SE	0.5	0.9
Median	-0.5	-1.0
Min, Max	-14, 10	-8, 8

Norfolk QoL-DN score = composite of 35 quality of life questions; lower scores indicate higher quality of life (range = -4 to 136). Nonmissing scores for items 27-33 imputed for patients who reported an impact due to COVID-19 pandemic. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 3.8
Norfolk Quality of Life - Diabetic Neuropathy (QoL-DN) Domain Scores: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Norfolk QoL-DN Domain: Symptoms

Sex: Male

Subgroup Visit	Vutrisiran (HELIOS-A) (N=79)	Patisiran (HELIOS-A) (N=27)
Month 18		
Actual Value		
n	74	23
Mean (SD)	10.4 (6.3)	10.6 (7.2)
SE	0.7	1.5
Median	9.0	10.0
Min, Max	1, 32	2, 23
Change from baseline		
n	72	23
Mean (SD)	-0.4 (5.5)	0.2 (5.1)
SE	0.6	1.1
Median	0.0	0.0
Min, Max	-16, 14	-10, 10

Norfolk QoL-DN score = composite of 35 quality of life questions; lower scores indicate higher quality of life (range = -4 to 136). Nonmissing scores for items 27-33 imputed for patients who reported an impact due to COVID-19 pandemic. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 3.8
Norfolk Quality of Life - Diabetic Neuropathy (QoL-DN) Domain Scores: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Norfolk QoL-DN Domain: Symptoms

Sex: Female

Subgroup Visit	Vutrisiran (HELIOS-A) (N=43)	Patisiran (HELIOS-A) (N=15)
Baseline		
n	43	15
Mean (SD)	11.2 (6.0)	11.1 (7.6)
SE	0.9	2.0
Median	10.0	12.0
Min, Max	0, 23	2, 24
Month 9		
Actual Value		
n	40	15
Mean (SD)	9.6 (5.4)	9.6 (7.5)
SE	0.8	1.9
Median	9.5	7.0
Min, Max	0, 25	1, 28
Change from baseline		
n	40	15
Mean (SD)	-1.5 (4.5)	-1.5 (6.0)
SE	0.7	1.5
Median	-1.0	0.0
Min, Max	-10, 6	-14, 11

Norfolk QoL-DN score = composite of 35 quality of life questions; lower scores indicate higher quality of life (range = -4 to 136). Nonmissing scores for items 27-33 imputed for patients who reported an impact due to COVID-19 pandemic. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 3.8
Norfolk Quality of Life - Diabetic Neuropathy (QoL-DN) Domain Scores: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Norfolk QoL-DN Domain: Symptoms

Sex: Female

Subgroup Visit	Vutrisiran (HELIOS-A) (N=43)	Patisiran (HELIOS-A) (N=15)
Month 18		
Actual Value		
n	40	15
Mean (SD)	9.0 (5.6)	10.1 (6.9)
SE	0.9	1.8
Median	9.0	9.0
Min, Max	0, 20	1, 24
Change from baseline		
n	40	15
Mean (SD)	-1.7 (5.2)	-1.1 (5.8)
SE	0.8	1.5
Median	-1.0	-1.0
Min, Max	-11, 9	-11, 8

Norfolk QoL-DN score = composite of 35 quality of life questions; lower scores indicate higher quality of life (range = -4 to 136). Nonmissing scores for items 27-33 imputed for patients who reported an impact due to COVID-19 pandemic. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 3.8
Norfolk Quality of Life - Diabetic Neuropathy (QoL-DN) Domain Scores: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Norfolk QoL-DN Domain: Symptoms

Race: White

Subgroup Visit	Vutrisiran (HELIOS-A) (N=86)	Patisiran (HELIOS-A) (N=29)
Baseline		
n	84	29
Mean (SD)	11.0 (6.3)	12.5 (7.5)
SE	0.7	1.4
Median	10.0	12.0
Min, Max	0, 31	0, 31
Month 9		
Actual Value		
n	82	28
Mean (SD)	9.8 (6.5)	11.3 (7.9)
SE	0.7	1.5
Median	8.5	10.5
Min, Max	0, 27	0, 28
Change from baseline		
n	80	28
Mean (SD)	-1.0 (4.3)	-1.5 (5.5)
SE	0.5	1.0
Median	-1.0	-1.0
Min, Max	-12, 10	-14, 11

Norfolk QoL-DN score = composite of 35 quality of life questions; lower scores indicate higher quality of life (range = -4 to 136). Nonmissing scores for items 27-33 imputed for patients who reported an impact due to COVID-19 pandemic. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 3.8
Norfolk Quality of Life - Diabetic Neuropathy (QoL-DN) Domain Scores: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Norfolk QoL-DN Domain: Symptoms

Race: White

Subgroup Visit	Vutrisiran (HELIOS-A) (N=86)	Patisiran (HELIOS-A) (N=29)
Month 18		
Actual Value		
n	81	27
Mean (SD)	9.3 (6.2)	11.1 (6.9)
SE	0.7	1.3
Median	9.0	10.0
Min, Max	0, 32	3, 23
Change from baseline		
n	79	27
Mean (SD)	-1.6 (4.9)	-0.9 (5.7)
SE	0.6	1.1
Median	-1.0	0.0
Min, Max	-11, 14	-11, 10

Norfolk QoL-DN score = composite of 35 quality of life questions; lower scores indicate higher quality of life (range = -4 to 136). Nonmissing scores for items 27-33 imputed for patients who reported an impact due to COVID-19 pandemic. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 3.8
Norfolk Quality of Life - Diabetic Neuropathy (QoL-DN) Domain Scores: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Norfolk QoL-DN Domain: Symptoms

Race: All Other Races

Subgroup Visit	Vutrisiran (HELIOS-A) (N=36)	Patisiran (HELIOS-A) (N=13)
Baseline		
n	36	13
Mean (SD)	10.9 (5.6)	8.4 (6.1)
SE	0.9	1.7
Median	10.0	7.0
Min, Max	2, 23	0, 20
Month 9		
Actual Value		
n	34	12
Mean (SD)	9.5 (5.7)	7.0 (4.1)
SE	1.0	1.2
Median	10.0	6.5
Min, Max	0, 31	1, 15
Change from baseline		
n	34	12
Mean (SD)	-1.4 (5.2)	-0.4 (3.5)
SE	0.9	1.0
Median	-1.0	-0.5
Min, Max	-14, 9	-7, 6

Norfolk QoL-DN score = composite of 35 quality of life questions; lower scores indicate higher quality of life (range = -4 to 136). Nonmissing scores for items 27-33 imputed for patients who reported an impact due to COVID-19 pandemic. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 3.8
Norfolk Quality of Life - Diabetic Neuropathy (QoL-DN) Domain Scores: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Norfolk QoL-DN Domain: Symptoms

Race: All Other Races

Subgroup Visit	Vutrisiran (HELIOS-A) (N=36)	Patisiran (HELIOS-A) (N=13)
Month 18		
Actual Value		
n	33	11
Mean (SD)	11.3 (5.5)	8.5 (7.4)
SE	1.0	2.2
Median	11.0	5.0
Min, Max	0, 20	1, 24
Change from baseline		
n	33	11
Mean (SD)	0.7 (6.2)	1.1 (4.2)
SE	1.1	1.3
Median	1.0	1.0
Min, Max	-16, 13	-5, 8

Norfolk QoL-DN score = composite of 35 quality of life questions; lower scores indicate higher quality of life (range = -4 to 136). Nonmissing scores for items 27-33 imputed for patients who reported an impact due to COVID-19 pandemic. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

Alnylam Pharmaceuticals Inc.
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Table 3.8
Norfolk Quality of Life - Diabetic Neuropathy (QoL-DN) Domain Scores: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Norfolk QoL-DN Domain: Symptoms

Region: North America

Subgroup Visit	Vutrisiran (HELIOS-A) (N=27)	Patisiran (HELIOS-A) (N=8)
Baseline		
n	26	8
Mean (SD)	10.5 (7.1)	9.6 (5.4)
SE	1.4	1.9
Median	8.5	8.0
Min, Max	0, 31	3, 18
Month 9		
Actual Value		
n	25	8
Mean (SD)	8.4 (6.0)	8.0 (5.1)
SE	1.2	1.8
Median	8.0	6.5
Min, Max	0, 26	3, 19
Change from baseline		
n	24	8
Mean (SD)	-1.9 (4.1)	-1.6 (4.5)
SE	0.8	1.6
Median	-2.5	-0.5
Min, Max	-10, 6	-8, 4

Norfolk QoL-DN score = composite of 35 quality of life questions; lower scores indicate higher quality of life (range = -4 to 136). Nonmissing scores for items 27-33 imputed for patients who reported an impact due to COVID-19 pandemic. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

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Table 3.8
Norfolk Quality of Life - Diabetic Neuropathy (QoL-DN) Domain Scores: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Norfolk QoL-DN Domain: Symptoms

Region: North America

Subgroup Visit	Vutrisiran (HELIOS-A) (N=27)	Patisiran (HELIOS-A) (N=8)
Month 18		
Actual Value		
n	25	7
Mean (SD)	9.6 (7.1)	8.9 (4.3)
SE	1.4	1.6
Median	7.0	9.0
Min, Max	0, 32	4, 16
Change from baseline		
n	24	7
Mean (SD)	-0.3 (4.7)	-1.1 (5.8)
SE	1.0	2.2
Median	-0.5	-2.0
Min, Max	-8, 13	-8, 5

Norfolk QoL-DN score = composite of 35 quality of life questions; lower scores indicate higher quality of life (range = -4 to 136). Nonmissing scores for items 27-33 imputed for patients who reported an impact due to COVID-19 pandemic. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 3.8
Norfolk Quality of Life - Diabetic Neuropathy (QoL-DN) Domain Scores: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Norfolk QoL-DN Domain: Symptoms

Region: Western Europe

Subgroup Visit	Vutrisiran (HELIOS-A) (N=42)	Patisiran (HELIOS-A) (N=20)
Baseline		
n	41	20
Mean (SD)	10.1 (5.2)	12.4 (6.5)
SE	0.8	1.5
Median	9.0	14.0
Min, Max	0, 20	0, 21
Month 9		
Actual Value		
n	39	18
Mean (SD)	8.6 (5.0)	11.3 (7.9)
SE	0.8	1.9
Median	9.0	11.5
Min, Max	0, 17	0, 28
Change from baseline		
n	38	18
Mean (SD)	-1.2 (4.4)	-1.1 (4.8)
SE	0.7	1.1
Median	-1.0	-1.5
Min, Max	-12, 10	-8, 11

Norfolk QoL-DN score = composite of 35 quality of life questions; lower scores indicate higher quality of life (range = -4 to 136). Nonmissing scores for items 27-33 imputed for patients who reported an impact due to COVID-19 pandemic. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 3.8
Norfolk Quality of Life - Diabetic Neuropathy (QoL-DN) Domain Scores: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Norfolk QoL-DN Domain: Symptoms

Region: Western Europe

Subgroup Visit	Vutrisiran (HELIOS-A) (N=42)	Patisiran (HELIOS-A) (N=20)
Month 18		
Actual Value		
n	39	18
Mean (SD)	8.7 (4.9)	12.1 (7.7)
SE	0.8	1.8
Median	9.0	10.5
Min, Max	1, 20	3, 24
Change from baseline		
n	38	18
Mean (SD)	-1.0 (5.3)	-0.3 (5.5)
SE	0.9	1.3
Median	-1.5	0.0
Min, Max	-11, 14	-10, 10

Norfolk QoL-DN score = composite of 35 quality of life questions; lower scores indicate higher quality of life (range = -4 to 136). Nonmissing scores for items 27-33 imputed for patients who reported an impact due to COVID-19 pandemic. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 3.8
Norfolk Quality of Life - Diabetic Neuropathy (QoL-DN) Domain Scores: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Norfolk QoL-DN Domain: Symptoms

Region: Rest of World

Subgroup Visit	Vutrisiran (HELIOS-A) (N=53)	Patisiran (HELIOS-A) (N=14)
Baseline		
n	53	14
Mean (SD)	11.9 (6.1)	10.4 (9.2)
SE	0.8	2.5
Median	10.0	9.0
Min, Max	1, 24	0, 31
Month 9		
Actual Value		
n	52	14
Mean (SD)	11.2 (7.0)	9.4 (7.4)
SE	1.0	2.0
Median	11.0	7.5
Min, Max	0, 31	1, 23
Change from baseline		
n	52	14
Mean (SD)	-0.8 (4.9)	-1.0 (5.7)
SE	0.7	1.5
Median	0.0	0.0
Min, Max	-14, 9	-14, 8

Norfolk QoL-DN score = composite of 35 quality of life questions; lower scores indicate higher quality of life (range = -4 to 136). Nonmissing scores for items 27-33 imputed for patients who reported an impact due to COVID-19 pandemic. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 3.8
Norfolk Quality of Life - Diabetic Neuropathy (QoL-DN) Domain Scores: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Norfolk QoL-DN Domain: Symptoms

Region: Rest of World

Subgroup Visit	Vutrisiran (HELIOS-A) (N=53)	Patisiran (HELIOS-A) (N=14)
Month 18		
Actual Value		
n	50	13
Mean (SD)	10.9 (6.2)	8.9 (7.1)
SE	0.9	2.0
Median	10.5	5.0
Min, Max	0, 23	1, 22
Change from baseline		
n	50	13
Mean (SD)	-1.1 (5.8)	0.1 (5.3)
SE	0.8	1.5
Median	0.0	0.0
Min, Max	-16, 12	-11, 10

Norfolk QoL-DN score = composite of 35 quality of life questions; lower scores indicate higher quality of life (range = -4 to 136). Nonmissing scores for items 27-33 imputed for patients who reported an impact due to COVID-19 pandemic. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 3.8
Norfolk Quality of Life - Diabetic Neuropathy (QoL-DN) Domain Scores: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Norfolk QoL-DN Domain: Symptoms

Baseline NIS: <50

Subgroup Visit	Vutrisiran (HELIOS-A) (N=78)	Patisiran (HELIOS-A) (N=27)
Baseline		
n	76	27
Mean (SD)	9.8 (6.0)	8.7 (5.9)
SE	0.7	1.1
Median	8.5	8.0
Min, Max	0, 31	0, 20
Month 9		
Actual Value		
n	77	27
Mean (SD)	7.8 (5.4)	7.3 (5.0)
SE	0.6	1.0
Median	7.0	6.0
Min, Max	0, 26	0, 19
Change from baseline		
n	75	27
Mean (SD)	-1.9 (4.3)	-1.4 (3.9)
SE	0.5	0.8
Median	-2.0	0.0
Min, Max	-14, 10	-8, 6

Norfolk QoL-DN score = composite of 35 quality of life questions; lower scores indicate higher quality of life (range = -4 to 136). Nonmissing scores for items 27-33 imputed for patients who reported an impact due to COVID-19 pandemic. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 3.8
Norfolk Quality of Life - Diabetic Neuropathy (QoL-DN) Domain Scores: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Norfolk QoL-DN Domain: Symptoms

Baseline NIS: <50

Subgroup Visit	Vutrisiran (HELIOS-A) (N=78)	Patisiran (HELIOS-A) (N=27)
Month 18		
Actual Value		
n	75	26
Mean (SD)	8.5 (6.1)	8.2 (5.9)
SE	0.7	1.2
Median	7.0	6.5
Min, Max	0, 32	1, 23
Change from baseline		
n	73	26
Mean (SD)	-0.9 (5.4)	-0.6 (4.9)
SE	0.6	1.0
Median	-1.0	-0.5
Min, Max	-16, 14	-10, 10

Norfolk QoL-DN score = composite of 35 quality of life questions; lower scores indicate higher quality of life (range = -4 to 136). Nonmissing scores for items 27-33 imputed for patients who reported an impact due to COVID-19 pandemic. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 3.8
Norfolk Quality of Life - Diabetic Neuropathy (QoL-DN) Domain Scores: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Norfolk QoL-DN Domain: Symptoms

Baseline NIS: ≥50

Subgroup Visit	Vutrisiran (HELIOS-A) (N=44)	Patisiran (HELIOS-A) (N=15)
Baseline		
n	44	15
Mean (SD)	13.1 (5.6)	15.7 (7.6)
SE	0.8	2.0
Median	12.5	16.0
Min, Max	0, 24	2, 31
Month 9		
Actual Value		
n	39	13
Mean (SD)	13.5 (6.0)	15.6 (7.9)
SE	1.0	2.2
Median	13.0	15.0
Min, Max	0, 31	4, 28
Change from baseline		
n	39	13
Mean (SD)	0.3 (4.7)	-0.5 (6.8)
SE	0.8	1.9
Median	1.0	-1.0
Min, Max	-10, 9	-14, 11

Norfolk QoL-DN score = composite of 35 quality of life questions; lower scores indicate higher quality of life (range = -4 to 136). Nonmissing scores for items 27-33 imputed for patients who reported an impact due to COVID-19 pandemic. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 3.8
Norfolk Quality of Life - Diabetic Neuropathy (QoL-DN) Domain Scores: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Norfolk QoL-DN Domain: Symptoms

Baseline NIS: ≥50

Subgroup Visit	Vutrisiran (HELIOS-A) (N=44)	Patisiran (HELIOS-A) (N=15)
Month 18		
Actual Value		
n	39	12
Mean (SD)	12.6 (5.0)	15.2 (7.1)
SE	0.8	2.1
Median	12.0	15.5
Min, Max	2, 23	4, 24
Change from baseline		
n	39	12
Mean (SD)	-0.8 (5.4)	0.3 (6.3)
SE	0.9	1.8
Median	0.0	0.0
Min, Max	-11, 12	-11, 10

Norfolk QoL-DN score = composite of 35 quality of life questions; lower scores indicate higher quality of life (range = -4 to 136). Nonmissing scores for items 27-33 imputed for patients who reported an impact due to COVID-19 pandemic. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 3.8
Norfolk Quality of Life - Diabetic Neuropathy (QoL-DN) Domain Scores: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Norfolk QoL-DN Domain: Symptoms

Previous Tetramer Stabilizer Use: Yes

Subgroup Visit	Vutrisiran (HELIOS-A) (N=75)	Patisiran (HELIOS-A) (N=33)
Baseline		
n	75	33
Mean (SD)	10.7 (6.0)	12.3 (7.5)
SE	0.7	1.3
Median	10.0	12.0
Min, Max	0, 31	0, 31
Month 9		
Actual Value		
n	74	32
Mean (SD)	9.9 (6.4)	10.8 (7.3)
SE	0.7	1.3
Median	9.5	10.0
Min, Max	0, 31	0, 28
Change from baseline		
n	74	32
Mean (SD)	-0.7 (4.8)	-1.2 (5.1)
SE	0.6	0.9
Median	-1.0	-1.0
Min, Max	-14, 10	-14, 11

Norfolk QoL-DN score = composite of 35 quality of life questions; lower scores indicate higher quality of life (range = -4 to 136). Nonmissing scores for items 27-33 imputed for patients who reported an impact due to COVID-19 pandemic. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 3.8
Norfolk Quality of Life - Diabetic Neuropathy (QoL-DN) Domain Scores: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Norfolk QoL-DN Domain: Symptoms

Previous Tetramer Stabilizer Use: Yes

Subgroup Visit	Vutrisiran (HELIOS-A) (N=75)	Patisiran (HELIOS-A) (N=33)
Month 18		
Actual Value		
n	71	31
Mean (SD)	9.9 (6.4)	11.3 (7.1)
SE	0.8	1.3
Median	9.0	10.0
Min, Max	0, 32	2, 24
Change from baseline		
n	71	31
Mean (SD)	-0.7 (5.4)	-0.1 (5.6)
SE	0.6	1.0
Median	0.0	0.0
Min, Max	-16, 14	-11, 10

Norfolk QoL-DN score = composite of 35 quality of life questions; lower scores indicate higher quality of life (range = -4 to 136). Nonmissing scores for items 27-33 imputed for patients who reported an impact due to COVID-19 pandemic. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 3.8
Norfolk Quality of Life - Diabetic Neuropathy (QoL-DN) Domain Scores: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Norfolk QoL-DN Domain: Symptoms

Previous Tetramer Stabilizer Use: No

Subgroup Visit	Vutrisiran (HELIOS-A) (N=47)	Patisiran (HELIOS-A) (N=9)
Baseline		
n	45	9
Mean (SD)	11.5 (6.2)	7.3 (5.0)
SE	0.9	1.7
Median	10.0	7.0
Min, Max	0, 24	2, 18
Month 9		
Actual Value		
n	42	8
Mean (SD)	9.3 (6.0)	6.6 (5.9)
SE	0.9	2.1
Median	9.0	5.0
Min, Max	0, 22	1, 19
Change from baseline		
n	40	8
Mean (SD)	-1.9 (4.1)	-0.9 (4.5)
SE	0.6	1.6
Median	-2.5	-0.5
Min, Max	-10, 6	-8, 6

Norfolk QoL-DN score = composite of 35 quality of life questions; lower scores indicate higher quality of life (range = -4 to 136). Nonmissing scores for items 27-33 imputed for patients who reported an impact due to COVID-19 pandemic. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 3.8
Norfolk Quality of Life - Diabetic Neuropathy (QoL-DN) Domain Scores: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Norfolk QoL-DN Domain: Symptoms

Previous Tetramer Stabilizer Use: No

Subgroup Visit	Vutrisiran (HELIOS-A) (N=47)	Patisiran (HELIOS-A) (N=9)
Month 18		
Actual Value		
n	43	7
Mean (SD)	9.8 (5.5)	6.4 (5.4)
SE	0.8	2.1
Median	9.0	4.0
Min, Max	0, 23	1, 16
Change from baseline		
n	41	7
Mean (SD)	-1.1 (5.5)	-1.1 (4.3)
SE	0.9	1.6
Median	-1.0	-2.0
Min, Max	-11, 13	-7, 5

Norfolk QoL-DN score = composite of 35 quality of life questions; lower scores indicate higher quality of life (range = -4 to 136). Nonmissing scores for items 27-33 imputed for patients who reported an impact due to COVID-19 pandemic. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 3.8
Norfolk Quality of Life - Diabetic Neuropathy (QoL-DN) Domain Scores: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Norfolk QoL-DN Domain: Symptoms

Genotype: V30M

Subgroup Visit	Vutrisiran (HELIOS-A) (N=54)	Patisiran (HELIOS-A) (N=20)
Baseline		
n	53	20
Mean (SD)	10.1 (5.6)	12.8 (5.9)
SE	0.8	1.3
Median	11.0	14.0
Min, Max	0, 20	2, 21
Month 9		
Actual Value		
n	52	20
Mean (SD)	8.8 (5.8)	11.8 (7.4)
SE	0.8	1.6
Median	8.0	11.5
Min, Max	0, 25	2, 28
Change from baseline		
n	51	20
Mean (SD)	-1.1 (4.5)	-1.0 (4.7)
SE	0.6	1.1
Median	-1.0	-1.0
Min, Max	-14, 7	-8, 11

Norfolk QoL-DN score = composite of 35 quality of life questions; lower scores indicate higher quality of life (range = -4 to 136). Nonmissing scores for items 27-33 imputed for patients who reported an impact due to COVID-19 pandemic. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 3.8
Norfolk Quality of Life - Diabetic Neuropathy (QoL-DN) Domain Scores: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Norfolk QoL-DN Domain: Symptoms

Genotype: V30M

Subgroup Visit	Vutrisiran (HELIOS-A) (N=54)	Patisiran (HELIOS-A) (N=20)
Month 18		
Actual Value		
n	52	20
Mean (SD)	8.2 (4.9)	12.2 (7.2)
SE	0.7	1.6
Median	9.0	10.5
Min, Max	0, 19	3, 24
Change from baseline		
n	51	20
Mean (SD)	-1.8 (5.1)	-0.6 (5.3)
SE	0.7	1.2
Median	-2.0	-0.5
Min, Max	-16, 12	-10, 10

Norfolk QoL-DN score = composite of 35 quality of life questions; lower scores indicate higher quality of life (range = -4 to 136). Nonmissing scores for items 27-33 imputed for patients who reported an impact due to COVID-19 pandemic. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 3.8
Norfolk Quality of Life - Diabetic Neuropathy (QoL-DN) Domain Scores: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Norfolk QoL-DN Domain: Symptoms

Genotype: non-V30M

Subgroup Visit	Vutrisiran (HELIOS-A) (N=68)	Patisiran (HELIOS-A) (N=22)
Baseline		
n	67	22
Mean (SD)	11.7 (6.4)	9.8 (8.2)
SE	0.8	1.8
Median	10.0	7.5
Min, Max	2, 31	0, 31
Month 9		
Actual Value		
n	64	20
Mean (SD)	10.4 (6.5)	8.2 (6.7)
SE	0.8	1.5
Median	9.0	6.5
Min, Max	0, 31	0, 23
Change from baseline		
n	63	20
Mean (SD)	-1.2 (4.6)	-1.3 (5.3)
SE	0.6	1.2
Median	-1.0	0.0
Min, Max	-10, 10	-14, 8

Norfolk QoL-DN score = composite of 35 quality of life questions; lower scores indicate higher quality of life (range = -4 to 136). Nonmissing scores for items 27-33 imputed for patients who reported an impact due to COVID-19 pandemic. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 3.8
Norfolk Quality of Life - Diabetic Neuropathy (QoL-DN) Domain Scores: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Norfolk QoL-DN Domain: Symptoms

Genotype: non-V30M

Subgroup Visit	Vutrisiran (HELIOS-A) (N=68)	Patisiran (HELIOS-A) (N=22)
Month 18		
Actual Value		
n	62	18
Mean (SD)	11.3 (6.6)	8.4 (6.4)
SE	0.8	1.5
Median	9.5	6.0
Min, Max	0, 32	1, 22
Change from baseline		
n	61	18
Mean (SD)	-0.1 (5.5)	0.0 (5.5)
SE	0.7	1.3
Median	1.0	0.5
Min, Max	-11, 14	-11, 10

Norfolk QoL-DN score = composite of 35 quality of life questions; lower scores indicate higher quality of life (range = -4 to 136). Nonmissing scores for items 27-33 imputed for patients who reported an impact due to COVID-19 pandemic. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 3.8
Norfolk Quality of Life - Diabetic Neuropathy (QoL-DN) Domain Scores: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Norfolk QoL-DN Domain: Symptoms

FAP Stage: I

Subgroup Visit	Vutrisiran (HELIOS-A) (N=84)	Patisiran (HELIOS-A) (N=31)
Baseline		
n	82	31
Mean (SD)	10.0 (5.8)	9.4 (6.6)
SE	0.6	1.2
Median	9.0	8.0
Min, Max	0, 31	0, 24
Month 9		
Actual Value		
n	82	30
Mean (SD)	8.5 (5.6)	7.8 (6.1)
SE	0.6	1.1
Median	8.0	6.0
Min, Max	0, 26	0, 28
Change from baseline		
n	80	30
Mean (SD)	-1.4 (4.4)	-1.6 (4.6)
SE	0.5	0.8
Median	-1.0	-0.5
Min, Max	-12, 10	-14, 7

Norfolk QoL-DN score = composite of 35 quality of life questions; lower scores indicate higher quality of life (range = -4 to 136). Nonmissing scores for items 27-33 imputed for patients who reported an impact due to COVID-19 pandemic. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

Alnylam Pharmaceuticals Inc.
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Table 3.8
Norfolk Quality of Life - Diabetic Neuropathy (QoL-DN) Domain Scores: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Norfolk QoL-DN Domain: Symptoms

FAP Stage: I

Subgroup Visit	Vutrisiran (HELIOS-A) (N=84)	Patisiran (HELIOS-A) (N=31)
Month 18		
Actual Value		
n	81	30
Mean (SD)	9.0 (6.1)	8.5 (6.2)
SE	0.7	1.1
Median	8.0	6.5
Min, Max	0, 32	1, 23
Change from baseline		
n	79	30
Mean (SD)	-0.7 (4.7)	-1.0 (4.9)
SE	0.5	0.9
Median	0.0	-0.5
Min, Max	-10, 14	-11, 10

Norfolk QoL-DN score = composite of 35 quality of life questions; lower scores indicate higher quality of life (range = -4 to 136). Nonmissing scores for items 27-33 imputed for patients who reported an impact due to COVID-19 pandemic. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

Alnylam Pharmaceuticals Inc.
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Table 3.8
Norfolk Quality of Life - Diabetic Neuropathy (QoL-DN) Domain Scores: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Norfolk QoL-DN Domain: Symptoms

FAP Stage: II&III

Subgroup Visit	Vutrisiran (HELIOS-A) (N=38)	Patisiran (HELIOS-A) (N=11)
Baseline		
n	38	11
Mean (SD)	13.2 (6.1)	16.5 (6.7)
SE	1.0	2.0
Median	12.5	16.0
Min, Max	0, 23	7, 31
Month 9		
Actual Value		
n	34	10
Mean (SD)	12.7 (6.9)	16.4 (6.6)
SE	1.2	2.1
Median	11.0	15.5
Min, Max	0, 31	6, 28
Change from baseline		
n	34	10
Mean (SD)	-0.6 (5.1)	0.3 (5.9)
SE	0.9	1.9
Median	0.5	-1.0
Min, Max	-14, 9	-8, 11

Norfolk QoL-DN score = composite of 35 quality of life questions; lower scores indicate higher quality of life (range = -4 to 136). Nonmissing scores for items 27-33 imputed for patients who reported an impact due to COVID-19 pandemic. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

Alnylam Pharmaceuticals Inc.
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Table 3.8
Norfolk Quality of Life - Diabetic Neuropathy (QoL-DN) Domain Scores: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Norfolk QoL-DN Domain: Symptoms

FAP Stage: II&III

Subgroup Visit	Vutrisiran (HELIOS-A) (N=38)	Patisiran (HELIOS-A) (N=11)
Month 18		
Actual Value		
n	33	8
Mean (SD)	12.0 (5.4)	17.6 (5.0)
SE	0.9	1.8
Median	11.0	17.0
Min, Max	2, 23	11, 24
Change from baseline		
n	33	8
Mean (SD)	-1.4 (6.7)	2.3 (6.4)
SE	1.2	2.3
Median	-1.0	2.5
Min, Max	-16, 13	-10, 10

Norfolk QoL-DN score = composite of 35 quality of life questions; lower scores indicate higher quality of life (range = -4 to 136). Nonmissing scores for items 27-33 imputed for patients who reported an impact due to COVID-19 pandemic. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

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Table 3.8
Norfolk Quality of Life - Diabetic Neuropathy (QoL-DN) Domain Scores: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Norfolk QoL-DN Domain: Symptoms

Cardiac Subpopulation: Yes

Subgroup Visit	Vutrisiran (HELIOS-A) (N=40)	Patisiran (HELIOS-A) (N=14)
Baseline		
n	40	14
Mean (SD)	11.9 (5.7)	13.7 (9.5)
SE	0.9	2.5
Median	10.0	14.0
Min, Max	0, 24	0, 31
Month 9		
Actual Value		
n	38	14
Mean (SD)	10.0 (5.9)	12.4 (8.5)
SE	0.9	2.3
Median	9.5	11.0
Min, Max	0, 27	0, 28
Change from baseline		
n	38	14
Mean (SD)	-2.0 (5.1)	-1.4 (6.1)
SE	0.8	1.6
Median	-0.5	0.0
Min, Max	-14, 7	-14, 8

Norfolk QoL-DN score = composite of 35 quality of life questions; lower scores indicate higher quality of life (range = -4 to 136). Nonmissing scores for items 27-33 imputed for patients who reported an impact due to COVID-19 pandemic. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

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Table 3.8
Norfolk Quality of Life - Diabetic Neuropathy (QoL-DN) Domain Scores: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Norfolk QoL-DN Domain: Symptoms

Cardiac Subpopulation: Yes

Subgroup Visit	Vutrisiran (HELIOS-A) (N=40)	Patisiran (HELIOS-A) (N=14)
Month 18		
Actual Value		
n	37	13
Mean (SD)	10.4 (5.4)	12.0 (6.9)
SE	0.9	1.9
Median	9.0	12.0
Min, Max	2, 22	2, 23
Change from baseline		
n	37	13
Mean (SD)	-1.8 (5.5)	-0.4 (6.7)
SE	0.9	1.8
Median	-2.0	2.0
Min, Max	-16, 11	-11, 10

Norfolk QoL-DN score = composite of 35 quality of life questions; lower scores indicate higher quality of life (range = -4 to 136). Nonmissing scores for items 27-33 imputed for patients who reported an impact due to COVID-19 pandemic. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

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Table 3.8
Norfolk Quality of Life - Diabetic Neuropathy (QoL-DN) Domain Scores: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Norfolk QoL-DN Domain: Symptoms

Cardiac Subpopulation: No

Subgroup Visit	Vutrisiran (HELIOS-A) (N=82)	Patisiran (HELIOS-A) (N=28)
Baseline		
n	80	28
Mean (SD)	10.5 (6.2)	10.0 (5.7)
SE	0.7	1.1
Median	10.0	8.5
Min, Max	0, 31	2, 20
Month 9		
Actual Value		
n	78	26
Mean (SD)	9.5 (6.5)	8.7 (6.2)
SE	0.7	1.2
Median	9.0	6.5
Min, Max	0, 31	1, 28
Change from baseline		
n	76	26
Mean (SD)	-0.7 (4.3)	-1.0 (4.3)
SE	0.5	0.8
Median	-1.0	-1.0
Min, Max	-10, 10	-8, 11

Norfolk QoL-DN score = composite of 35 quality of life questions; lower scores indicate higher quality of life (range = -4 to 136). Nonmissing scores for items 27-33 imputed for patients who reported an impact due to COVID-19 pandemic. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 3.8
Norfolk Quality of Life - Diabetic Neuropathy (QoL-DN) Domain Scores: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Norfolk QoL-DN Domain: Symptoms

Cardiac Subpopulation: No

Subgroup Visit	Vutrisiran (HELIOS-A) (N=82)	Patisiran (HELIOS-A) (N=28)
Month 18		
Actual Value		
n	77	25
Mean (SD)	9.7 (6.3)	9.6 (7.1)
SE	0.7	1.4
Median	9.0	8.0
Min, Max	0, 32	1, 24
Change from baseline		
n	75	25
Mean (SD)	-0.4 (5.3)	-0.3 (4.7)
SE	0.6	0.9
Median	0.0	0.0
Min, Max	-11, 14	-8, 10

Norfolk QoL-DN score = composite of 35 quality of life questions; lower scores indicate higher quality of life (range = -4 to 136). Nonmissing scores for items 27-33 imputed for patients who reported an impact due to COVID-19 pandemic. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 3.8
Norfolk Quality of Life - Diabetic Neuropathy (QoL-DN) Domain Scores: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Norfolk QoL-DN Domain: Symptoms

Weight (kg): <65

Subgroup Visit	Vutrisiran (HELIOS-A) (N=46)	Patisiran (HELIOS-A) (N=15)
Baseline		
n	46	15
Mean (SD)	10.2 (5.0)	10.9 (7.7)
SE	0.7	2.0
Median	9.5	12.0
Min, Max	0, 22	2, 24
Month 9		
Actual Value		
n	44	15
Mean (SD)	9.7 (4.6)	9.5 (5.4)
SE	0.7	1.4
Median	9.5	8.0
Min, Max	0, 20	2, 19
Change from baseline		
n	44	15
Mean (SD)	-0.6 (4.2)	-1.4 (5.2)
SE	0.6	1.3
Median	0.0	0.0
Min, Max	-14, 7	-14, 6

Norfolk QoL-DN score = composite of 35 quality of life questions; lower scores indicate higher quality of life (range = -4 to 136). Nonmissing scores for items 27-33 imputed for patients who reported an impact due to COVID-19 pandemic. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

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Table 3.8
Norfolk Quality of Life - Diabetic Neuropathy (QoL-DN) Domain Scores: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Norfolk QoL-DN Domain: Symptoms

Weight (kg): <65

Subgroup Visit	Vutrisiran (HELIOS-A) (N=46)	Patisiran (HELIOS-A) (N=15)
Month 18		
Actual Value		
n	42	15
Mean (SD)	10.5 (5.4)	10.0 (6.6)
SE	0.8	1.7
Median	10.5	8.0
Min, Max	0, 20	3, 24
Change from baseline		
n	42	15
Mean (SD)	0.2 (5.3)	-0.9 (5.1)
SE	0.8	1.3
Median	1.0	0.0
Min, Max	-16, 12	-11, 8

Norfolk QoL-DN score = composite of 35 quality of life questions; lower scores indicate higher quality of life (range = -4 to 136). Nonmissing scores for items 27-33 imputed for patients who reported an impact due to COVID-19 pandemic. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

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Table 3.8
Norfolk Quality of Life - Diabetic Neuropathy (QoL-DN) Domain Scores: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Norfolk QoL-DN Domain: Symptoms

Weight (kg): ≥65

Subgroup Visit	Vutrisiran (HELIOS-A) (N=76)	Patisiran (HELIOS-A) (N=27)
Baseline		
n	74	27
Mean (SD)	11.5 (6.6)	11.4 (7.2)
SE	0.8	1.4
Median	10.5	10.0
Min, Max	0, 31	0, 31
Month 9		
Actual Value		
n	72	25
Mean (SD)	9.7 (7.1)	10.3 (8.2)
SE	0.8	1.6
Median	8.5	10.0
Min, Max	0, 31	0, 28
Change from baseline		
n	70	25
Mean (SD)	-1.5 (4.8)	-1.0 (4.9)
SE	0.6	1.0
Median	-1.5	-1.0
Min, Max	-12, 10	-8, 11

Norfolk QoL-DN score = composite of 35 quality of life questions; lower scores indicate higher quality of life (range = -4 to 136). Nonmissing scores for items 27-33 imputed for patients who reported an impact due to COVID-19 pandemic. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

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Table 3.8
Norfolk Quality of Life - Diabetic Neuropathy (QoL-DN) Domain Scores: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Norfolk QoL-DN Domain: Symptoms

Weight (kg): ≥65

Subgroup Visit	Vutrisiran (HELIOS-A) (N=76)	Patisiran (HELIOS-A) (N=27)
Month 18		
Actual Value		
n	72	23
Mean (SD)	9.5 (6.4)	10.7 (7.4)
SE	0.8	1.6
Median	8.5	9.0
Min, Max	0, 32	1, 23
Change from baseline		
n	70	23
Mean (SD)	-1.5 (5.4)	0.0 (5.6)
SE	0.6	1.2
Median	-2.0	0.0
Min, Max	-11, 14	-10, 10

Norfolk QoL-DN score = composite of 35 quality of life questions; lower scores indicate higher quality of life (range = -4 to 136). Nonmissing scores for items 27-33 imputed for patients who reported an impact due to COVID-19 pandemic. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

Norfolk-QoL-DN – Domäne Kleine Nervenfasern

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Table 3.5
Norfolk Quality of Life - Diabetic Neuropathy (QoL-DN) Domain Scores: Change from Baseline to Month 18, MMRM Model
Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A) Subgroup Analysis
mITT Population

Norfolk QoL-DN Domain: Small Fiber

Subgroup Visit	LS Mean (95% CI) Vutrisiran (HELIOS-A) (N=122)	LS Mean (95% CI) Patisiran (HELIOS-A) (N=42)	LS Mean Difference (Vutrisiran-Patisiran) (95% CI), p-value	Standardized Effect Size (95% CI)
Age (years)				
<65	74	30		
Month 9	0.32 (-0.32, 0.96)	-0.24 (-1.25, 0.77)	0.56 (-0.63, 1.76), 0.3529	0.20 (-0.23, 0.62)
Month 18	0.67 (-0.01, 1.36)	-0.07 (-1.18, 1.04)	0.74 (-0.56, 2.04), 0.2641	0.23 (-0.20, 0.65)
≥65	43	10		
Month 9	-0.42 (-1.25, 0.41)	0.70 (-0.99, 2.39)	-1.12 (-3.00, 0.76), 0.2416	-0.40 (-1.09, 0.28)
Month 18	-0.07 (-0.94, 0.80)	0.87 (-0.89, 2.63)	-0.94 (-2.91, 1.02), 0.3447	-0.33 (-1.04, 0.39)
p-value of Treatment*Age	0.1269			

Norfolk QoL-DN score = composite of 35 quality of life questions; lower scores indicate higher quality of life (range = -4 to 136). Nonmissing scores for items 27-33 imputed for patients who reported an impact due to COVID-19 pandemic. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.
LS estimates and p-value derived from mixed-effects model for repeated measures (MMRM), controlling for categorical factors (treatment, visit), the subgroup variable, continuous covariate (baseline value), and interaction (treatment by visit, treatment by subgroup).
Standardized effect size (d) = LS mean difference/estimated pooled standard deviation with the small sample bias correction.

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

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Table 3.5
Norfolk Quality of Life - Diabetic Neuropathy (QoL-DN) Domain Scores: Change from Baseline to Month 18, MMRM Model
Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A) Subgroup Analysis
mITT Population

Norfolk QoL-DN Domain: Small Fiber

Subgroup Visit	LS Mean (95% CI) Vutrisiran (HELIOS-A) (N=122)	LS Mean (95% CI) Patisiran (HELIOS-A) (N=42)	LS Mean Difference (Vutrisiran-Patisiran) (95% CI), p-value	Standardized Effect Size (95% CI)
Sex				
Male	76	25		
Month 9	0.15 (-0.49, 0.79)	0.23 (-0.87, 1.34)	-0.08 (-1.36, 1.20), 0.8998	-0.03 (-0.48, 0.42)
Month 18	0.51 (-0.17, 1.19)	0.41 (-0.78, 1.60)	0.10 (-1.27, 1.47), 0.8875	0.03 (-0.43, 0.50)
Female	41	15		
Month 9	-0.13 (-0.98, 0.72)	-0.41 (-1.82, 0.99)	0.28 (-1.36, 1.93), 0.7359	0.11 (-0.48, 0.69)
Month 18	0.22 (-0.66, 1.10)	-0.24 (-1.70, 1.22)	0.46 (-1.24, 2.17), 0.5939	0.16 (-0.43, 0.74)
p-value of Treatment*Sex	0.7209			

Norfolk QoL-DN score = composite of 35 quality of life questions; lower scores indicate higher quality of life (range = -4 to 136). Nonmissing scores for items 27-33 imputed for patients who reported an impact due to COVID-19 pandemic. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.
LS estimates and p-value derived from mixed-effects model for repeated measures (MMRM), controlling for categorical factors (treatment, visit), the subgroup variable, continuous covariate (baseline value), and interaction (treatment by visit, treatment by subgroup).
Standardized effect size (d) = LS mean difference/estimated pooled standard deviation with the small sample bias correction.

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Table 3.5
Norfolk Quality of Life - Diabetic Neuropathy (QoL-DN) Domain Scores: Change from Baseline to Month 18, MMRM Model
Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A) Subgroup Analysis
mITT Population

Norfolk QoL-DN Domain: Small Fiber

Subgroup Visit	LS Mean (95% CI) Vutrisiran (HELIOS-A) (N=122)	LS Mean (95% CI) Patisiran (HELIOS-A) (N=42)	LS Mean Difference (Vutrisiran-Patisiran) (95% CI), p-value	Standardized Effect Size (95% CI)
Race				
White	82	28		
Month 9	0.01 (-0.61, 0.62)	-0.05 (-1.11, 1.01)	0.06 (-1.17, 1.28), 0.9273	0.02 (-0.41, 0.45)
Month 18	0.36 (-0.30, 1.02)	0.12 (-1.02, 1.26)	0.24 (-1.08, 1.56), 0.7202	0.07 (-0.36, 0.51)
All Other Races	35	12		
Month 9	0.16 (-0.76, 1.09)	0.08 (-1.48, 1.65)	0.08 (-1.73, 1.89), 0.9309	0.02 (-0.62, 0.67)
Month 18	0.52 (-0.44, 1.47)	0.25 (-1.38, 1.88)	0.26 (-1.62, 2.15), 0.7834	0.09 (-0.58, 0.76)
p-value of Treatment*Race	0.9828			

Norfolk QoL-DN score = composite of 35 quality of life questions; lower scores indicate higher quality of life (range = -4 to 136). Nonmissing scores for items 27-33 imputed for patients who reported an impact due to COVID-19 pandemic. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.
LS estimates and p-value derived from mixed-effects model for repeated measures (MMRM), controlling for categorical factors (treatment, visit), the subgroup variable, continuous covariate (baseline value), and interaction (treatment by visit, treatment by subgroup).
Standardized effect size (d) = LS mean difference/estimated pooled standard deviation with the small sample bias correction.

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Table 3.5
Norfolk Quality of Life - Diabetic Neuropathy (QoL-DN) Domain Scores: Change from Baseline to Month 18, MMRM Model
Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A) Subgroup Analysis
mITT Population

Norfolk QoL-DN Domain: Small Fiber

Subgroup Visit	LS Mean (95% CI) Vutrisiran (HELIOS-A) (N=122)	LS Mean (95% CI) Patisiran (HELIOS-A) (N=42)	LS Mean Difference (Vutrisiran-Patisiran) (95% CI), p-value	Standardized Effect Size (95% CI)
Region				
North America	26	8		
Month 9	-0.40 (-1.50, 0.69)	-1.07 (-2.97, 0.84)	0.66 (-1.52, 2.85), 0.5498	0.26 (-0.52, 1.04)
Month 18	-0.05 (-1.17, 1.07)	-0.90 (-2.87, 1.06)	0.86 (-1.39, 3.11), 0.4529	0.27 (-0.56, 1.09)
Western Europe	39	18		
Month 9	0.12 (-0.75, 0.99)	0.21 (-1.09, 1.50)	-0.08 (-1.64, 1.47), 0.9144	-0.03 (-0.58, 0.52)
Month 18	0.48 (-0.43, 1.38)	0.37 (-0.99, 1.73)	0.11 (-1.51, 1.73), 0.8945	0.03 (-0.52, 0.59)
Rest of World	52	14		
Month 9	0.21 (-0.54, 0.97)	0.34 (-1.11, 1.79)	-0.13 (-1.76, 1.51), 0.8799	-0.04 (-0.63, 0.54)
Month 18	0.57 (-0.23, 1.37)	0.50 (-1.02, 2.02)	0.07 (-1.65, 1.78), 0.9372	0.02 (-0.58, 0.62)
p-value of Treatment*Region	0.8208			

Norfolk QoL-DN score = composite of 35 quality of life questions; lower scores indicate higher quality of life (range = -4 to 136). Nonmissing scores for items 27-33 imputed for patients who reported an impact due to COVID-19 pandemic. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.
LS estimates and p-value derived from mixed-effects model for repeated measures (MMRM), controlling for categorical factors (treatment, visit), the subgroup variable, continuous covariate (baseline value), and interaction (treatment by visit, treatment by subgroup).
Standardized effect size (d) = LS mean difference/estimated pooled standard deviation with the small sample bias correction.

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Table 3.5
Norfolk Quality of Life - Diabetic Neuropathy (QoL-DN) Domain Scores: Change from Baseline to Month 18, MMRM Model
Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A) Subgroup Analysis
mITT Population

Norfolk QoL-DN Domain: Small Fiber

Subgroup Visit	LS Mean (95% CI) Vutrisiran (HELIOS-A) (N=122)	LS Mean (95% CI) Patisiran (HELIOS-A) (N=42)	LS Mean Difference (Vutrisiran-Patisiran) (95% CI), p-value	Standardized Effect Size (95% CI)
Baseline NIS				
<50	76	27		
Month 9	-0.59 (-1.22, 0.03)	-0.74 (-1.76, 0.28)	0.15 (-1.05, 1.34), 0.8093	0.06 (-0.38, 0.49)
Month 18	-0.24 (-0.91, 0.43)	-0.56 (-1.67, 0.54)	0.32 (-0.96, 1.61), 0.6210	0.12 (-0.33, 0.56)
≥50	41	13		
Month 9	1.23 (0.39, 2.07)	1.61 (0.18, 3.04)	-0.38 (-2.02, 1.26), 0.6505	-0.12 (-0.74, 0.50)
Month 18	1.58 (0.72, 2.45)	1.78 (0.29, 3.28)	-0.20 (-1.91, 1.51), 0.8183	-0.06 (-0.69, 0.58)
p-value of Treatment*Baseline NIS	0.5980			

Norfolk QoL-DN score = composite of 35 quality of life questions; lower scores indicate higher quality of life (range = -4 to 136). Nonmissing scores for items 27-33 imputed for patients who reported an impact due to COVID-19 pandemic. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.
LS estimates and p-value derived from mixed-effects model for repeated measures (MMRM), controlling for categorical factors (treatment, visit), the subgroup variable, continuous covariate (baseline value), and interaction (treatment by visit, treatment by subgroup).
Standardized effect size (d) = LS mean difference/estimated pooled standard deviation with the small sample bias correction.

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Table 3.5
Norfolk Quality of Life - Diabetic Neuropathy (QoL-DN) Domain Scores: Change from Baseline to Month 18, MMRM Model
Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A) Subgroup Analysis
mITT Population

Norfolk QoL-DN Domain: Small Fiber

Subgroup Visit	LS Mean (95% CI) Vutrisiran (HELIOS-A) (N=122)	LS Mean (95% CI) Patisiran (HELIOS-A) (N=42)	LS Mean Difference (Vutrisiran-Patisiran) (95% CI), p-value	Standardized Effect Size (95% CI)
Previous Tetramer Stabilizer Use				
Yes	74	32		
Month 9	0.36 (-0.27, 1.00)	0.27 (-0.71, 1.26)	0.09 (-1.08, 1.26), 0.8823	0.03 (-0.38, 0.44)
Month 18	0.72 (0.04, 1.41)	0.44 (-0.64, 1.51)	0.29 (-0.98, 1.56), 0.6542	0.09 (-0.33, 0.51)
No	43	8		
Month 9	-0.51 (-1.34, 0.32)	-1.10 (-2.99, 0.79)	0.59 (-1.46, 2.65), 0.5692	0.26 (-0.49, 1.00)
Month 18	-0.14 (-1.00, 0.71)	-0.94 (-2.89, 1.01)	0.79 (-1.32, 2.91), 0.4607	0.28 (-0.51, 1.07)
p-value of Treatment*Previous Tetramer Stabilizer Use	0.6657			

Norfolk QoL-DN score = composite of 35 quality of life questions; lower scores indicate higher quality of life (range = -4 to 136). Nonmissing scores for items 27-33 imputed for patients who reported an impact due to COVID-19 pandemic. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.
LS estimates and p-value derived from mixed-effects model for repeated measures (MMRM), controlling for categorical factors (treatment, visit), the subgroup variable, continuous covariate (baseline value), and interaction (treatment by visit, treatment by subgroup).
Standardized effect size (d) = LS mean difference/estimated pooled standard deviation with the small sample bias correction.

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Table 3.5
Norfolk Quality of Life - Diabetic Neuropathy (QoL-DN) Domain Scores: Change from Baseline to Month 18, MMRM Model
Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A) Subgroup Analysis
mITT Population

Norfolk QoL-DN Domain: Small Fiber

Subgroup Visit	LS Mean (95% CI) Vutrisiran (HELIOS-A) (N=122)	LS Mean (95% CI) Patisiran (HELIOS-A) (N=42)	LS Mean Difference (Vutrisiran-Patisiran) (95% CI), p-value	Standardized Effect Size (95% CI)
Genotype				
V30M	52	20		
Month 9	-0.12 (-0.88, 0.65)	1.06 (-0.16, 2.28)	-1.17 (-2.59, 0.24), 0.1034	-0.38 (-0.90, 0.13)
Month 18	0.24 (-0.56, 1.04)	1.21 (-0.08, 2.49)	-0.97 (-2.46, 0.52), 0.2023	-0.30 (-0.81, 0.22)
non-V30M	65	20		
Month 9	0.18 (-0.51, 0.88)	-1.06 (-2.27, 0.14)	1.25 (-0.13, 2.63), 0.0765	0.48 (-0.03, 0.98)
Month 18	0.54 (-0.20, 1.28)	-0.92 (-2.21, 0.38)	1.45 (-0.02, 2.93), 0.0532	0.49 (-0.04, 1.01)
p-value of Treatment*Genotype	0.0127			

Norfolk QoL-DN score = composite of 35 quality of life questions; lower scores indicate higher quality of life (range = -4 to 136). Nonmissing scores for items 27-33 imputed for patients who reported an impact due to COVID-19 pandemic. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.
LS estimates and p-value derived from mixed-effects model for repeated measures (MMRM), controlling for categorical factors (treatment, visit), the subgroup variable, continuous covariate (baseline value), and interaction (treatment by visit, treatment by subgroup).
Standardized effect size (d) = LS mean difference/estimated pooled standard deviation with the small sample bias correction.

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Table 3.5
Norfolk Quality of Life - Diabetic Neuropathy (QoL-DN) Domain Scores: Change from Baseline to Month 18, MMRM Model
Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A) Subgroup Analysis
mITT Population

Norfolk QoL-DN Domain: Small Fiber

Subgroup Visit	LS Mean (95% CI) Vutrisiran (HELIOS-A) (N=122)	LS Mean (95% CI) Patisiran (HELIOS-A) (N=42)	LS Mean Difference (Vutrisiran-Patisiran) (95% CI), p-value	Standardized Effect Size (95% CI)
FAP Stage				
I	82	30		
Month 9	-0.25 (-0.86, 0.36)	-0.53 (-1.53, 0.48)	0.28 (-0.90, 1.45), 0.6421	0.10 (-0.32, 0.51)
Month 18	0.11 (-0.54, 0.76)	-0.32 (-1.40, 0.75)	0.43 (-0.82, 1.69), 0.4968	0.15 (-0.27, 0.57)
II&III	35	10		
Month 9	0.75 (-0.15, 1.65)	1.58 (-0.10, 3.26)	-0.83 (-2.73, 1.07), 0.3905	-0.30 (-0.99, 0.40)
Month 18	1.11 (0.18, 2.04)	1.78 (0.03, 3.53)	-0.67 (-2.65, 1.30), 0.5030	-0.19 (-0.95, 0.57)
p-value of Treatment*FAP Stage	0.3143			

Norfolk QoL-DN score = composite of 35 quality of life questions; lower scores indicate higher quality of life (range = -4 to 136). Nonmissing scores for items 27-33 imputed for patients who reported an impact due to COVID-19 pandemic. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.
LS estimates and p-value derived from mixed-effects model for repeated measures (MMRM), controlling for categorical factors (treatment, visit), the subgroup variable, continuous covariate (baseline value), and interaction (treatment by visit, treatment by subgroup).
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Table 3.5
Norfolk Quality of Life - Diabetic Neuropathy (QoL-DN) Domain Scores: Change from Baseline to Month 18, MMRM Model
Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A) Subgroup Analysis
mITT Population

Norfolk QoL-DN Domain: Small Fiber

Subgroup Visit	LS Mean (95% CI) Vutrisiran (HELIOS-A) (N=122)	LS Mean (95% CI) Patisiran (HELIOS-A) (N=42)	LS Mean Difference (Vutrisiran-Patisiran) (95% CI), p-value	Standardized Effect Size (95% CI)
Cardiac Subpopulation				
Yes	38	14		
Month 9	0.33 (-0.55, 1.21)	0.17 (-1.28, 1.62)	0.16 (-1.55, 1.86), 0.8553	0.05 (-0.55, 0.66)
Month 18	0.68 (-0.23, 1.59)	0.34 (-1.18, 1.86)	0.34 (-1.43, 2.12), 0.7047	0.10 (-0.52, 0.72)
No	79	26		
Month 9	-0.08 (-0.71, 0.55)	-0.11 (-1.19, 0.98)	0.02 (-1.23, 1.28), 0.9692	0.01 (-0.43, 0.45)
Month 18	0.27 (-0.40, 0.95)	0.06 (-1.10, 1.23)	0.21 (-1.14, 1.56), 0.7602	0.07 (-0.38, 0.52)
p-value of Treatment*Cardiac Subpopulation	0.8979			

Norfolk QoL-DN score = composite of 35 quality of life questions; lower scores indicate higher quality of life (range = -4 to 136). Nonmissing scores for items 27-33 imputed for patients who reported an impact due to COVID-19 pandemic. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.
LS estimates and p-value derived from mixed-effects model for repeated measures (MMRM), controlling for categorical factors (treatment, visit), the subgroup variable, continuous covariate (baseline value), and interaction (treatment by visit, treatment by subgroup).
Standardized effect size (d) = LS mean difference/estimated pooled standard deviation with the small sample bias correction.

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Table 3.5
Norfolk Quality of Life - Diabetic Neuropathy (QoL-DN) Domain Scores: Change from Baseline to Month 18, MMRM Model
Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A) Subgroup Analysis
mITT Population

Norfolk QoL-DN Domain: Small Fiber

Subgroup Visit	LS Mean (95% CI) Vutrisiran (HELIOS-A) (N=122)	LS Mean (95% CI) Patisiran (HELIOS-A) (N=42)	LS Mean Difference (Vutrisiran-Patisiran) (95% CI), p-value	Standardized Effect Size (95% CI)
Weight (kg)				
<65	44	15		
Month 9	0.20 (-0.61, 1.02)	-0.23 (-1.63, 1.17)	0.43 (-1.19, 2.05), 0.6014	0.15 (-0.43, 0.73)
Month 18	0.56 (-0.30, 1.42)	-0.05 (-1.52, 1.41)	0.61 (-1.08, 2.31), 0.4772	0.18 (-0.40, 0.77)
≥65	73	25		
Month 9	-0.04 (-0.69, 0.61)	0.12 (-0.98, 1.23)	-0.16 (-1.45, 1.12), 0.8024	-0.06 (-0.51, 0.40)
Month 18	0.31 (-0.38, 1.01)	0.29 (-0.91, 1.49)	0.02 (-1.37, 1.41), 0.9775	0.01 (-0.46, 0.47)
p-value of Treatment*Weight	0.5581			

Norfolk QoL-DN score = composite of 35 quality of life questions; lower scores indicate higher quality of life (range = -4 to 136). Nonmissing scores for items 27-33 imputed for patients who reported an impact due to COVID-19 pandemic. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.
LS estimates and p-value derived from mixed-effects model for repeated measures (MMRM), controlling for categorical factors (treatment, visit), the subgroup variable, continuous covariate (baseline value), and interaction (treatment by visit, treatment by subgroup).
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Table 3.8
Norfolk Quality of Life - Diabetic Neuropathy (QoL-DN) Domain Scores: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Norfolk QoL-DN Domain: Small Fiber

Age (years): <65

Subgroup Visit	Vutrisiran (HELIOS-A) (N=76)	Patisiran (HELIOS-A) (N=31)
Baseline		
n	75	31
Mean (SD)	4.9 (4.2)	5.1 (4.3)
SE	0.5	0.8
Median	4.0	4.0
Min, Max	0, 15	0, 14
Month 9		
Actual Value		
n	74	30
Mean (SD)	5.1 (4.2)	4.8 (4.4)
SE	0.5	0.8
Median	4.0	4.5
Min, Max	0, 15	0, 14
Change from baseline		
n	73	30
Mean (SD)	0.3 (3.1)	-0.4 (3.0)
SE	0.4	0.6
Median	0.0	0.0
Min, Max	-8, 10	-8, 4

Norfolk QoL-DN score = composite of 35 quality of life questions; lower scores indicate higher quality of life (range = -4 to 136). Nonmissing scores for items 27-33 imputed for patients who reported an impact due to COVID-19 pandemic. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 3.8
Norfolk Quality of Life - Diabetic Neuropathy (QoL-DN) Domain Scores: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Norfolk QoL-DN Domain: Small Fiber

Age (years): <65

Subgroup Visit	Vutrisiran (HELIOS-A) (N=76)	Patisiran (HELIOS-A) (N=31)
Month 18		
Actual Value		
n	74	29
Mean (SD)	5.4 (4.8)	4.9 (4.4)
SE	0.6	0.8
Median	5.0	6.0
Min, Max	0, 16	0, 14
Change from baseline		
n	73	29
Mean (SD)	0.5 (3.3)	0.0 (3.6)
SE	0.4	0.7
Median	0.0	0.0
Min, Max	-12, 9	-8, 7

Norfolk QoL-DN score = composite of 35 quality of life questions; lower scores indicate higher quality of life (range = -4 to 136). Nonmissing scores for items 27-33 imputed for patients who reported an impact due to COVID-19 pandemic. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 3.8
Norfolk Quality of Life - Diabetic Neuropathy (QoL-DN) Domain Scores: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Norfolk QoL-DN Domain: Small Fiber

Age (years): ≥65

Subgroup Visit	Vutrisiran (HELIOS-A) (N=46)	Patisiran (HELIOS-A) (N=11)
Baseline		
n	46	11
Mean (SD)	4.1 (4.2)	5.0 (5.3)
SE	0.6	1.6
Median	3.0	4.0
Min, Max	0, 16	0, 16
Month 9		
Actual Value		
n	42	10
Mean (SD)	3.5 (3.6)	5.9 (5.9)
SE	0.6	1.9
Median	2.0	4.0
Min, Max	0, 15	0, 15
Change from baseline		
n	42	10
Mean (SD)	-0.3 (2.8)	0.8 (4.1)
SE	0.4	1.3
Median	0.0	0.0
Min, Max	-8, 7	-5, 10

Norfolk QoL-DN score = composite of 35 quality of life questions; lower scores indicate higher quality of life (range = -4 to 136). Nonmissing scores for items 27-33 imputed for patients who reported an impact due to COVID-19 pandemic. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 3.8
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mITT Population

Norfolk QoL-DN Domain: Small Fiber

Age (years): ≥65

Subgroup Visit	Vutrisiran (HELIOS-A) (N=46)	Patisiran (HELIOS-A) (N=11)
Month 18		
Actual Value		
n	40	9
Mean (SD)	4.2 (3.9)	6.0 (5.3)
SE	0.6	1.8
Median	3.0	6.0
Min, Max	0, 13	0, 15
Change from baseline		
n	40	9
Mean (SD)	0.6 (3.3)	0.6 (2.6)
SE	0.5	0.9
Median	0.0	0.0
Min, Max	-10, 6	-2, 6

Norfolk QoL-DN score = composite of 35 quality of life questions; lower scores indicate higher quality of life (range = -4 to 136). Nonmissing scores for items 27-33 imputed for patients who reported an impact due to COVID-19 pandemic. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 3.8
Norfolk Quality of Life - Diabetic Neuropathy (QoL-DN) Domain Scores: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Norfolk QoL-DN Domain: Small Fiber

Sex: Male

Subgroup Visit	Vutrisiran (HELIOS-A) (N=79)	Patisiran (HELIOS-A) (N=27)
Baseline		
n	78	27
Mean (SD)	4.7 (4.2)	4.8 (4.1)
SE	0.5	0.8
Median	4.0	4.0
Min, Max	0, 15	0, 14
Month 9		
Actual Value		
n	76	25
Mean (SD)	4.6 (4.2)	4.9 (4.5)
SE	0.5	0.9
Median	4.0	5.0
Min, Max	0, 15	0, 14
Change from baseline		
n	75	25
Mean (SD)	0.0 (3.1)	0.0 (3.7)
SE	0.4	0.7
Median	0.0	0.0
Min, Max	-8, 10	-8, 10

Norfolk QoL-DN score = composite of 35 quality of life questions; lower scores indicate higher quality of life (range = -4 to 136). Nonmissing scores for items 27-33 imputed for patients who reported an impact due to COVID-19 pandemic. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 3.8
Norfolk Quality of Life - Diabetic Neuropathy (QoL-DN) Domain Scores: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Norfolk QoL-DN Domain: Small Fiber

Sex: Male

Subgroup Visit	Vutrisiran (HELIOS-A) (N=79)	Patisiran (HELIOS-A) (N=27)
Month 18		
Actual Value		
n	74	23
Mean (SD)	5.4 (4.6)	5.3 (4.1)
SE	0.5	0.9
Median	5.0	6.0
Min, Max	0, 16	0, 12
Change from baseline		
n	73	23
Mean (SD)	0.8 (3.4)	0.7 (3.3)
SE	0.4	0.7
Median	0.0	0.0
Min, Max	-12, 9	-6, 7

Norfolk QoL-DN score = composite of 35 quality of life questions; lower scores indicate higher quality of life (range = -4 to 136). Nonmissing scores for items 27-33 imputed for patients who reported an impact due to COVID-19 pandemic. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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mITT Population

Norfolk QoL-DN Domain: Small Fiber

Sex: Female

Subgroup Visit	Vutrisiran (HELIOS-A) (N=43)	Patisiran (HELIOS-A) (N=15)
Baseline		
n	43	15
Mean (SD)	4.3 (4.3)	5.7 (5.4)
SE	0.7	1.4
Median	3.0	4.0
Min, Max	0, 16	0, 16
Month 9		
Actual Value		
n	40	15
Mean (SD)	4.5 (3.9)	5.3 (5.2)
SE	0.6	1.3
Median	3.5	4.0
Min, Max	0, 13	0, 15
Change from baseline		
n	40	15
Mean (SD)	0.2 (2.9)	-0.4 (2.6)
SE	0.5	0.7
Median	0.0	0.0
Min, Max	-8, 7	-8, 2

Norfolk QoL-DN score = composite of 35 quality of life questions; lower scores indicate higher quality of life (range = -4 to 136). Nonmissing scores for items 27-33 imputed for patients who reported an impact due to COVID-19 pandemic. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 3.8
Norfolk Quality of Life - Diabetic Neuropathy (QoL-DN) Domain Scores: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Norfolk QoL-DN Domain: Small Fiber

Sex: Female

Subgroup Visit	Vutrisiran (HELIOS-A) (N=43)	Patisiran (HELIOS-A) (N=15)
Month 18		
Actual Value		
n	40	15
Mean (SD)	4.2 (4.2)	4.8 (5.3)
SE	0.7	1.4
Median	3.0	3.0
Min, Max	0, 16	0, 15
Change from baseline		
n	40	15
Mean (SD)	0.0 (3.0)	-0.9 (3.3)
SE	0.5	0.9
Median	0.0	0.0
Min, Max	-10, 6	-8, 3

Norfolk QoL-DN score = composite of 35 quality of life questions; lower scores indicate higher quality of life (range = -4 to 136). Nonmissing scores for items 27-33 imputed for patients who reported an impact due to COVID-19 pandemic. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Norfolk Quality of Life - Diabetic Neuropathy (QoL-DN) Domain Scores: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Norfolk QoL-DN Domain: Small Fiber

Race: White

Subgroup Visit	Vutrisiran (HELIOS-A) (N=86)	Patisiran (HELIOS-A) (N=29)
Baseline		
n	85	29
Mean (SD)	5.0 (4.4)	5.7 (4.6)
SE	0.5	0.9
Median	4.0	4.0
Min, Max	0, 16	0, 16
Month 9		
Actual Value		
n	82	28
Mean (SD)	4.8 (4.1)	5.5 (4.6)
SE	0.5	0.9
Median	4.0	5.0
Min, Max	0, 15	0, 15
Change from baseline		
n	81	28
Mean (SD)	-0.1 (3.0)	-0.3 (3.0)
SE	0.3	0.6
Median	0.0	0.0
Min, Max	-8, 7	-8, 4

Norfolk QoL-DN score = composite of 35 quality of life questions; lower scores indicate higher quality of life (range = -4 to 136). Nonmissing scores for items 27-33 imputed for patients who reported an impact due to COVID-19 pandemic. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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mITT Population

Norfolk QoL-DN Domain: Small Fiber

Race: White

Subgroup Visit	Vutrisiran (HELIOS-A) (N=86)	Patisiran (HELIOS-A) (N=29)
Month 18		
Actual Value		
n	81	27
Mean (SD)	5.2 (4.6)	5.3 (4.4)
SE	0.5	0.9
Median	5.0	6.0
Min, Max	0, 16	0, 15
Change from baseline		
n	80	27
Mean (SD)	0.3 (3.5)	-0.2 (3.7)
SE	0.4	0.7
Median	0.0	0.0
Min, Max	-12, 9	-8, 7

Norfolk QoL-DN score = composite of 35 quality of life questions; lower scores indicate higher quality of life (range = -4 to 136). Nonmissing scores for items 27-33 imputed for patients who reported an impact due to COVID-19 pandemic. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

Alnylam Pharmaceuticals Inc.
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Table 3.8
Norfolk Quality of Life - Diabetic Neuropathy (QoL-DN) Domain Scores: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Norfolk QoL-DN Domain: Small Fiber

Race: All Other Races

Subgroup Visit	Vutrisiran (HELIOS-A) (N=36)	Patisiran (HELIOS-A) (N=13)
Baseline		
n	36	13
Mean (SD)	3.6 (3.7)	3.7 (4.3)
SE	0.6	1.2
Median	2.5	2.0
Min, Max	0, 12	0, 11
Month 9		
Actual Value		
n	34	12
Mean (SD)	3.9 (3.9)	3.9 (5.0)
SE	0.7	1.5
Median	2.5	1.0
Min, Max	0, 12	0, 14
Change from baseline		
n	34	12
Mean (SD)	0.4 (3.0)	0.2 (4.2)
SE	0.5	1.2
Median	0.0	0.0
Min, Max	-8, 10	-8, 10

Norfolk QoL-DN score = composite of 35 quality of life questions; lower scores indicate higher quality of life (range = -4 to 136). Nonmissing scores for items 27-33 imputed for patients who reported an impact due to COVID-19 pandemic. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 3.8
Norfolk Quality of Life - Diabetic Neuropathy (QoL-DN) Domain Scores: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Norfolk QoL-DN Domain: Small Fiber

Race: All Other Races

Subgroup Visit	Vutrisiran (HELIOS-A) (N=36)	Patisiran (HELIOS-A) (N=13)
Month 18		
Actual Value		
n	33	11
Mean (SD)	4.4 (4.3)	4.8 (5.0)
SE	0.7	1.5
Median	3.0	6.0
Min, Max	0, 13	0, 14
Change from baseline		
n	33	11
Mean (SD)	0.9 (2.8)	0.9 (2.2)
SE	0.5	0.7
Median	0.0	0.0
Min, Max	-4, 9	-1, 6

Norfolk QoL-DN score = composite of 35 quality of life questions; lower scores indicate higher quality of life (range = -4 to 136). Nonmissing scores for items 27-33 imputed for patients who reported an impact due to COVID-19 pandemic. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 3.8
Norfolk Quality of Life - Diabetic Neuropathy (QoL-DN) Domain Scores: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Norfolk QoL-DN Domain: Small Fiber

Region: North America

Subgroup Visit	Vutrisiran (HELIOS-A) (N=27)	Patisiran (HELIOS-A) (N=8)
Baseline		
n	26	8
Mean (SD)	2.3 (3.7)	3.8 (4.7)
SE	0.7	1.7
Median	1.0	1.5
Min, Max	0, 14	0, 12
Month 9		
Actual Value		
n	25	8
Mean (SD)	2.3 (2.7)	3.1 (4.9)
SE	0.5	1.7
Median	1.0	0.5
Min, Max	0, 8	0, 14
Change from baseline		
n	24	8
Mean (SD)	0.3 (2.8)	-0.6 (3.1)
SE	0.6	1.1
Median	0.0	-0.5
Min, Max	-8, 7	-6, 4

Norfolk QoL-DN score = composite of 35 quality of life questions; lower scores indicate higher quality of life (range = -4 to 136). Nonmissing scores for items 27-33 imputed for patients who reported an impact due to COVID-19 pandemic. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 3.8
Norfolk Quality of Life - Diabetic Neuropathy (QoL-DN) Domain Scores: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Norfolk QoL-DN Domain: Small Fiber

Region: North America

Subgroup Visit	Vutrisiran (HELIOS-A) (N=27)	Patisiran (HELIOS-A) (N=8)
Month 18		
Actual Value		
n	25	7
Mean (SD)	2.8 (3.6)	3.1 (3.8)
SE	0.7	1.4
Median	2.0	2.0
Min, Max	0, 13	0, 10
Change from baseline		
n	24	7
Mean (SD)	0.5 (3.3)	-0.9 (4.8)
SE	0.7	1.8
Median	0.0	0.0
Min, Max	-12, 5	-8, 6

Norfolk QoL-DN score = composite of 35 quality of life questions; lower scores indicate higher quality of life (range = -4 to 136). Nonmissing scores for items 27-33 imputed for patients who reported an impact due to COVID-19 pandemic. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 3.8
Norfolk Quality of Life - Diabetic Neuropathy (QoL-DN) Domain Scores: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Norfolk QoL-DN Domain: Small Fiber

Region: Western Europe

Subgroup Visit	Vutrisiran (HELIOS-A) (N=42)	Patisiran (HELIOS-A) (N=20)
Baseline		
n	42	20
Mean (SD)	5.7 (4.5)	6.2 (4.4)
SE	0.7	1.0
Median	5.0	5.5
Min, Max	0, 16	0, 16
Month 9		
Actual Value		
n	39	18
Mean (SD)	5.3 (4.3)	6.1 (4.5)
SE	0.7	1.1
Median	4.0	6.0
Min, Max	0, 15	0, 15
Change from baseline		
n	39	18
Mean (SD)	-0.2 (3.4)	-0.3 (3.1)
SE	0.5	0.7
Median	0.0	0.0
Min, Max	-8, 7	-8, 4

Norfolk QoL-DN score = composite of 35 quality of life questions; lower scores indicate higher quality of life (range = -4 to 136). Nonmissing scores for items 27-33 imputed for patients who reported an impact due to COVID-19 pandemic. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 3.8
Norfolk Quality of Life - Diabetic Neuropathy (QoL-DN) Domain Scores: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Norfolk QoL-DN Domain: Small Fiber

Region: Western Europe

Subgroup Visit	Vutrisiran (HELIOS-A) (N=42)	Patisiran (HELIOS-A) (N=20)
Month 18		
Actual Value		
n	39	18
Mean (SD)	6.0 (4.6)	6.4 (4.5)
SE	0.7	1.1
Median	6.0	7.0
Min, Max	0, 16	0, 15
Change from baseline		
n	39	18
Mean (SD)	0.4 (3.3)	0.0 (3.3)
SE	0.5	0.8
Median	0.0	-0.5
Min, Max	-10, 7	-8, 5

Norfolk QoL-DN score = composite of 35 quality of life questions; lower scores indicate higher quality of life (range = -4 to 136). Nonmissing scores for items 27-33 imputed for patients who reported an impact due to COVID-19 pandemic. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 3.8
Norfolk Quality of Life - Diabetic Neuropathy (QoL-DN) Domain Scores: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Norfolk QoL-DN Domain: Small Fiber

Region: Rest of World

Subgroup Visit	Vutrisiran (HELIOS-A) (N=53)	Patisiran (HELIOS-A) (N=14)
Baseline		
n	53	14
Mean (SD)	4.8 (3.9)	4.4 (4.6)
SE	0.5	1.2
Median	4.0	3.0
Min, Max	0, 13	0, 14
Month 9		
Actual Value		
n	52	14
Mean (SD)	5.1 (4.1)	4.8 (4.9)
SE	0.6	1.3
Median	4.5	4.0
Min, Max	0, 12	0, 14
Change from baseline		
n	52	14
Mean (SD)	0.2 (2.8)	0.4 (3.9)
SE	0.4	1.0
Median	0.0	0.0
Min, Max	-8, 10	-8, 10

Norfolk QoL-DN score = composite of 35 quality of life questions; lower scores indicate higher quality of life (range = -4 to 136). Nonmissing scores for items 27-33 imputed for patients who reported an impact due to COVID-19 pandemic. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 3.8
Norfolk Quality of Life - Diabetic Neuropathy (QoL-DN) Domain Scores: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Norfolk QoL-DN Domain: Small Fiber

Region: Rest of World

Subgroup Visit	Vutrisiran (HELIOS-A) (N=53)	Patisiran (HELIOS-A) (N=14)
Month 18		
Actual Value		
n	50	13
Mean (SD)	5.3 (4.5)	4.4 (4.8)
SE	0.6	1.3
Median	5.0	4.0
Min, Max	0, 16	0, 14
Change from baseline		
n	50	13
Mean (SD)	0.6 (3.3)	0.8 (2.6)
SE	0.5	0.7
Median	0.0	0.0
Min, Max	-7, 9	-4, 7

Norfolk QoL-DN score = composite of 35 quality of life questions; lower scores indicate higher quality of life (range = -4 to 136). Nonmissing scores for items 27-33 imputed for patients who reported an impact due to COVID-19 pandemic. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 3.8
Norfolk Quality of Life - Diabetic Neuropathy (QoL-DN) Domain Scores: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Norfolk QoL-DN Domain: Small Fiber

Baseline NIS: <50

Subgroup Visit	Vutrisiran (HELIOS-A) (N=78)	Patisiran (HELIOS-A) (N=27)
Baseline		
n	77	27
Mean (SD)	3.3 (3.4)	4.6 (4.4)
SE	0.4	0.8
Median	2.0	4.0
Min, Max	0, 14	0, 12
Month 9		
Actual Value		
n	77	27
Mean (SD)	3.2 (3.2)	3.8 (4.4)
SE	0.4	0.8
Median	2.0	2.0
Min, Max	0, 13	0, 14
Change from baseline		
n	76	27
Mean (SD)	0.0 (2.6)	-0.8 (3.1)
SE	0.3	0.6
Median	0.0	0.0
Min, Max	-8, 7	-8, 4

Norfolk QoL-DN score = composite of 35 quality of life questions; lower scores indicate higher quality of life (range = -4 to 136). Nonmissing scores for items 27-33 imputed for patients who reported an impact due to COVID-19 pandemic. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 3.8
Norfolk Quality of Life - Diabetic Neuropathy (QoL-DN) Domain Scores: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Norfolk QoL-DN Domain: Small Fiber

Baseline NIS: <50

Subgroup Visit	Vutrisiran (HELIOS-A) (N=78)	Patisiran (HELIOS-A) (N=27)
Month 18		
Actual Value		
n	75	26
Mean (SD)	3.4 (3.6)	4.4 (4.6)
SE	0.4	0.9
Median	2.0	3.0
Min, Max	0, 13	0, 14
Change from baseline		
n	74	26
Mean (SD)	0.1 (2.7)	-0.3 (3.4)
SE	0.3	0.7
Median	0.0	0.0
Min, Max	-12, 7	-8, 6

Norfolk QoL-DN score = composite of 35 quality of life questions; lower scores indicate higher quality of life (range = -4 to 136). Nonmissing scores for items 27-33 imputed for patients who reported an impact due to COVID-19 pandemic. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 3.8
Norfolk Quality of Life - Diabetic Neuropathy (QoL-DN) Domain Scores: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Norfolk QoL-DN Domain: Small Fiber

Baseline NIS: ≥50

Subgroup Visit	Vutrisiran (HELIOS-A) (N=44)	Patisiran (HELIOS-A) (N=15)
Baseline		
n	44	15
Mean (SD)	7.0 (4.5)	5.9 (4.8)
SE	0.7	1.2
Median	7.5	4.0
Min, Max	0, 16	0, 16
Month 9		
Actual Value		
n	39	13
Mean (SD)	7.3 (4.2)	7.6 (4.6)
SE	0.7	1.3
Median	8.0	7.0
Min, Max	0, 15	0, 15
Change from baseline		
n	39	13
Mean (SD)	0.3 (3.6)	1.3 (3.5)
SE	0.6	1.0
Median	0.0	1.0
Min, Max	-8, 10	-5, 10

Norfolk QoL-DN score = composite of 35 quality of life questions; lower scores indicate higher quality of life (range = -4 to 136). Nonmissing scores for items 27-33 imputed for patients who reported an impact due to COVID-19 pandemic. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 3.8
Norfolk Quality of Life - Diabetic Neuropathy (QoL-DN) Domain Scores: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Norfolk QoL-DN Domain: Small Fiber

Baseline NIS: ≥50

Subgroup Visit	Vutrisiran (HELIOS-A) (N=44)	Patisiran (HELIOS-A) (N=15)
Month 18		
Actual Value		
n	39	12
Mean (SD)	8.1 (4.5)	6.8 (4.2)
SE	0.7	1.2
Median	8.0	7.5
Min, Max	0, 16	0, 15
Change from baseline		
n	39	12
Mean (SD)	1.3 (4.1)	1.1 (3.3)
SE	0.6	0.9
Median	1.0	0.0
Min, Max	-10, 9	-4, 7

Norfolk QoL-DN score = composite of 35 quality of life questions; lower scores indicate higher quality of life (range = -4 to 136). Nonmissing scores for items 27-33 imputed for patients who reported an impact due to COVID-19 pandemic. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 3.8
Norfolk Quality of Life - Diabetic Neuropathy (QoL-DN) Domain Scores: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Norfolk QoL-DN Domain: Small Fiber

Previous Tetramer Stabilizer Use: Yes

Subgroup Visit	Vutrisiran (HELIOS-A) (N=75)	Patisiran (HELIOS-A) (N=33)
Baseline		
n	75	33
Mean (SD)	4.9 (4.1)	5.8 (4.7)
SE	0.5	0.8
Median	4.0	4.0
Min, Max	0, 16	0, 16
Month 9		
Actual Value		
n	74	32
Mean (SD)	5.1 (4.2)	5.9 (4.8)
SE	0.5	0.9
Median	4.0	5.5
Min, Max	0, 15	0, 15
Change from baseline		
n	74	32
Mean (SD)	0.2 (3.2)	0.0 (3.4)
SE	0.4	0.6
Median	0.0	0.0
Min, Max	-8, 10	-8, 10

Norfolk QoL-DN score = composite of 35 quality of life questions; lower scores indicate higher quality of life (range = -4 to 136). Nonmissing scores for items 27-33 imputed for patients who reported an impact due to COVID-19 pandemic. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 3.8
Norfolk Quality of Life - Diabetic Neuropathy (QoL-DN) Domain Scores: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Norfolk QoL-DN Domain: Small Fiber

Previous Tetramer Stabilizer Use: Yes

Subgroup Visit	Vutrisiran (HELIOS-A) (N=75)	Patisiran (HELIOS-A) (N=33)
Month 18		
Actual Value		
n	71	31
Mean (SD)	5.9 (4.6)	5.6 (4.6)
SE	0.5	0.8
Median	6.0	6.0
Min, Max	0, 16	0, 15
Change from baseline		
n	71	31
Mean (SD)	0.9 (3.4)	0.1 (3.4)
SE	0.4	0.6
Median	0.0	0.0
Min, Max	-10, 9	-8, 7

Norfolk QoL-DN score = composite of 35 quality of life questions; lower scores indicate higher quality of life (range = -4 to 136). Nonmissing scores for items 27-33 imputed for patients who reported an impact due to COVID-19 pandemic. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 3.8
Norfolk Quality of Life - Diabetic Neuropathy (QoL-DN) Domain Scores: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Norfolk QoL-DN Domain: Small Fiber

Previous Tetramer Stabilizer Use: No

Subgroup Visit	Vutrisiran (HELIOS-A) (N=47)	Patisiran (HELIOS-A) (N=9)
Baseline		
n	46	9
Mean (SD)	4.0 (4.4)	2.7 (3.1)
SE	0.6	1.0
Median	2.0	2.0
Min, Max	0, 14	0, 9
Month 9		
Actual Value		
n	42	8
Mean (SD)	3.5 (3.7)	1.8 (2.5)
SE	0.6	0.9
Median	2.0	0.0
Min, Max	0, 12	0, 6
Change from baseline		
n	41	8
Mean (SD)	-0.1 (2.6)	-0.8 (3.1)
SE	0.4	1.1
Median	0.0	-0.5
Min, Max	-8, 7	-6, 4

Norfolk QoL-DN score = composite of 35 quality of life questions; lower scores indicate higher quality of life (range = -4 to 136). Nonmissing scores for items 27-33 imputed for patients who reported an impact due to COVID-19 pandemic. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 3.8
Norfolk Quality of Life - Diabetic Neuropathy (QoL-DN) Domain Scores: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Norfolk QoL-DN Domain: Small Fiber

Previous Tetramer Stabilizer Use: No

Subgroup Visit	Vutrisiran (HELIOS-A) (N=47)	Patisiran (HELIOS-A) (N=9)
Month 18		
Actual Value		
n	43	7
Mean (SD)	3.6 (3.9)	2.9 (4.0)
SE	0.6	1.5
Median	2.0	0.0
Min, Max	0, 13	0, 10
Change from baseline		
n	42	7
Mean (SD)	-0.2 (3.0)	0.3 (3.6)
SE	0.5	1.4
Median	0.0	0.0
Min, Max	-12, 5	-6, 6

Norfolk QoL-DN score = composite of 35 quality of life questions; lower scores indicate higher quality of life (range = -4 to 136). Nonmissing scores for items 27-33 imputed for patients who reported an impact due to COVID-19 pandemic. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 3.8
Norfolk Quality of Life - Diabetic Neuropathy (QoL-DN) Domain Scores: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Norfolk QoL-DN Domain: Small Fiber

Genotype: V30M

Subgroup Visit	Vutrisiran (HELIOS-A) (N=54)	Patisiran (HELIOS-A) (N=20)
Baseline		
n	53	20
Mean (SD)	6.4 (4.3)	6.7 (4.4)
SE	0.6	1.0
Median	7.0	7.0
Min, Max	0, 16	1, 16
Month 9		
Actual Value		
n	52	20
Mean (SD)	5.6 (4.2)	7.1 (4.1)
SE	0.6	0.9
Median	4.5	6.5
Min, Max	0, 15	1, 15
Change from baseline		
n	51	20
Mean (SD)	-0.6 (3.4)	0.4 (3.4)
SE	0.5	0.8
Median	0.0	0.5
Min, Max	-8, 7	-5, 10

Norfolk QoL-DN score = composite of 35 quality of life questions; lower scores indicate higher quality of life (range = -4 to 136). Nonmissing scores for items 27-33 imputed for patients who reported an impact due to COVID-19 pandemic. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 3.8
Norfolk Quality of Life - Diabetic Neuropathy (QoL-DN) Domain Scores: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Norfolk QoL-DN Domain: Small Fiber

Genotype: V30M

Subgroup Visit	Vutrisiran (HELIOS-A) (N=54)	Patisiran (HELIOS-A) (N=20)
Month 18		
Actual Value		
n	52	20
Mean (SD)	6.1 (4.7)	7.6 (4.0)
SE	0.7	0.9
Median	6.0	7.5
Min, Max	0, 16	0, 15
Change from baseline		
n	51	20
Mean (SD)	-0.1 (3.7)	0.9 (2.6)
SE	0.5	0.6
Median	0.0	1.0
Min, Max	-12, 7	-5, 5

Norfolk QoL-DN score = composite of 35 quality of life questions; lower scores indicate higher quality of life (range = -4 to 136). Nonmissing scores for items 27-33 imputed for patients who reported an impact due to COVID-19 pandemic. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 3.8
Norfolk Quality of Life - Diabetic Neuropathy (QoL-DN) Domain Scores: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Norfolk QoL-DN Domain: Small Fiber

Genotype: non-V30M

Subgroup Visit	Vutrisiran (HELIOS-A) (N=68)	Patisiran (HELIOS-A) (N=22)
Baseline		
n	68	22
Mean (SD)	3.2 (3.6)	3.6 (4.3)
SE	0.4	0.9
Median	2.0	2.0
Min, Max	0, 14	0, 14
Month 9		
Actual Value		
n	64	20
Mean (SD)	3.7 (3.8)	3.0 (4.5)
SE	0.5	1.0
Median	2.0	0.5
Min, Max	0, 12	0, 14
Change from baseline		
n	64	20
Mean (SD)	0.7 (2.5)	-0.7 (3.2)
SE	0.3	0.7
Median	0.0	0.0
Min, Max	-4, 10	-8, 4

Norfolk QoL-DN score = composite of 35 quality of life questions; lower scores indicate higher quality of life (range = -4 to 136). Nonmissing scores for items 27-33 imputed for patients who reported an impact due to COVID-19 pandemic. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

Alnylam Pharmaceuticals Inc.
ALN-TTRSC02-002

Table 3.8
Norfolk Quality of Life - Diabetic Neuropathy (QoL-DN) Domain Scores: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Norfolk QoL-DN Domain: Small Fiber

Genotype: non-V30M

Subgroup Visit	Vutrisiran (HELIOS-A) (N=68)	Patisiran (HELIOS-A) (N=22)
Month 18		
Actual Value		
n	62	18
Mean (SD)	4.0 (4.1)	2.4 (3.5)
SE	0.5	0.8
Median	2.5	0.0
Min, Max	0, 13	0, 9
Change from baseline		
n	62	18
Mean (SD)	1.0 (2.8)	-0.7 (3.9)
SE	0.4	0.9
Median	0.0	0.0
Min, Max	-5, 9	-8, 7

Norfolk QoL-DN score = composite of 35 quality of life questions; lower scores indicate higher quality of life (range = -4 to 136). Nonmissing scores for items 27-33 imputed for patients who reported an impact due to COVID-19 pandemic. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

Alnylam Pharmaceuticals Inc.
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Table 3.8
Norfolk Quality of Life - Diabetic Neuropathy (QoL-DN) Domain Scores: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Norfolk QoL-DN Domain: Small Fiber

FAP Stage: I

Subgroup Visit	Vutrisiran (HELIOS-A) (N=84)	Patisiran (HELIOS-A) (N=31)
Baseline		
n	83	31
Mean (SD)	4.1 (4.1)	4.8 (4.2)
SE	0.4	0.8
Median	3.0	4.0
Min, Max	0, 15	0, 12
Month 9		
Actual Value		
n	82	30
Mean (SD)	4.0 (3.8)	4.3 (4.6)
SE	0.4	0.8
Median	3.0	3.0
Min, Max	0, 15	0, 14
Change from baseline		
n	81	30
Mean (SD)	0.0 (2.9)	-0.5 (3.6)
SE	0.3	0.7
Median	0.0	0.0
Min, Max	-8, 7	-8, 10

Norfolk QoL-DN score = composite of 35 quality of life questions; lower scores indicate higher quality of life (range = -4 to 136). Nonmissing scores for items 27-33 imputed for patients who reported an impact due to COVID-19 pandemic. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

Alnylam Pharmaceuticals Inc.
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Table 3.8
Norfolk Quality of Life - Diabetic Neuropathy (QoL-DN) Domain Scores: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Norfolk QoL-DN Domain: Small Fiber

FAP Stage: I

Subgroup Visit	Vutrisiran (HELIOS-A) (N=84)	Patisiran (HELIOS-A) (N=31)
Month 18		
Actual Value		
n	81	30
Mean (SD)	4.2 (4.2)	4.4 (4.6)
SE	0.5	0.8
Median	3.0	3.0
Min, Max	0, 15	0, 14
Change from baseline		
n	80	30
Mean (SD)	0.2 (2.9)	-0.4 (3.2)
SE	0.3	0.6
Median	0.0	0.0
Min, Max	-12, 7	-8, 5

Norfolk QoL-DN score = composite of 35 quality of life questions; lower scores indicate higher quality of life (range = -4 to 136). Nonmissing scores for items 27-33 imputed for patients who reported an impact due to COVID-19 pandemic. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

Alnylam Pharmaceuticals Inc.
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Table 3.8
Norfolk Quality of Life - Diabetic Neuropathy (QoL-DN) Domain Scores: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Norfolk QoL-DN Domain: Small Fiber

FAP Stage: II&III

Subgroup Visit	Vutrisiran (HELIOS-A) (N=38)	Patisiran (HELIOS-A) (N=11)
Baseline		
n	38	11
Mean (SD)	5.7 (4.4)	5.9 (5.4)
SE	0.7	1.6
Median	5.0	3.0
Min, Max	0, 16	0, 16
Month 9		
Actual Value		
n	34	10
Mean (SD)	6.0 (4.4)	7.2 (4.8)
SE	0.7	1.5
Median	6.0	6.5
Min, Max	0, 15	0, 15
Change from baseline		
n	34	10
Mean (SD)	0.3 (3.2)	1.0 (2.0)
SE	0.5	0.6
Median	0.0	1.0
Min, Max	-8, 10	-2, 4

Norfolk QoL-DN score = composite of 35 quality of life questions; lower scores indicate higher quality of life (range = -4 to 136). Nonmissing scores for items 27-33 imputed for patients who reported an impact due to COVID-19 pandemic. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

Alnylam Pharmaceuticals Inc.
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Table 3.8
Norfolk Quality of Life - Diabetic Neuropathy (QoL-DN) Domain Scores: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Norfolk QoL-DN Domain: Small Fiber

FAP Stage: II&III

Subgroup Visit	Vutrisiran (HELIOS-A) (N=38)	Patisiran (HELIOS-A) (N=11)
Month 18		
Actual Value		
n	33	8
Mean (SD)	6.8 (4.6)	7.9 (3.5)
SE	0.8	1.2
Median	6.0	7.5
Min, Max	0, 16	3, 15
Change from baseline		
n	33	8
Mean (SD)	1.2 (4.0)	2.1 (3.3)
SE	0.7	1.2
Median	0.0	0.5
Min, Max	-10, 9	-1, 7

Norfolk QoL-DN score = composite of 35 quality of life questions; lower scores indicate higher quality of life (range = -4 to 136). Nonmissing scores for items 27-33 imputed for patients who reported an impact due to COVID-19 pandemic. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

Alnylam Pharmaceuticals Inc.
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Table 3.8
Norfolk Quality of Life - Diabetic Neuropathy (QoL-DN) Domain Scores: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Norfolk QoL-DN Domain: Small Fiber

Cardiac Subpopulation: Yes

Subgroup Visit	Vutrisiran (HELIOS-A) (N=40)	Patisiran (HELIOS-A) (N=14)
Baseline		
n	40	14
Mean (SD)	4.3 (3.9)	6.1 (5.5)
SE	0.6	1.5
Median	2.5	5.0
Min, Max	0, 13	0, 16
Month 9		
Actual Value		
n	38	14
Mean (SD)	4.5 (4.4)	5.7 (5.2)
SE	0.7	1.4
Median	2.5	4.5
Min, Max	0, 15	0, 15
Change from baseline		
n	38	14
Mean (SD)	0.2 (3.0)	-0.4 (3.2)
SE	0.5	0.8
Median	0.0	0.0
Min, Max	-5, 10	-8, 4

Norfolk QoL-DN score = composite of 35 quality of life questions; lower scores indicate higher quality of life (range = -4 to 136). Nonmissing scores for items 27-33 imputed for patients who reported an impact due to COVID-19 pandemic. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

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Table 3.8
Norfolk Quality of Life - Diabetic Neuropathy (QoL-DN) Domain Scores: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Norfolk QoL-DN Domain: Small Fiber

Cardiac Subpopulation: Yes

Subgroup Visit	Vutrisiran (HELIOS-A) (N=40)	Patisiran (HELIOS-A) (N=14)
Month 18		
Actual Value		
n	37	13
Mean (SD)	5.4 (4.8)	5.8 (5.1)
SE	0.8	1.4
Median	5.0	6.0
Min, Max	0, 16	0, 15
Change from baseline		
n	37	13
Mean (SD)	1.1 (3.5)	0.4 (3.0)
SE	0.6	0.8
Median	0.0	0.0
Min, Max	-5, 9	-4, 7

Norfolk QoL-DN score = composite of 35 quality of life questions; lower scores indicate higher quality of life (range = -4 to 136). Nonmissing scores for items 27-33 imputed for patients who reported an impact due to COVID-19 pandemic. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

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Table 3.8
Norfolk Quality of Life - Diabetic Neuropathy (QoL-DN) Domain Scores: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Norfolk QoL-DN Domain: Small Fiber

Cardiac Subpopulation: No

Subgroup Visit	Vutrisiran (HELIOS-A) (N=82)	Patisiran (HELIOS-A) (N=28)
Baseline		
n	81	28
Mean (SD)	4.8 (4.4)	4.6 (4.0)
SE	0.5	0.8
Median	4.0	3.5
Min, Max	0, 16	0, 12
Month 9		
Actual Value		
n	78	26
Mean (SD)	4.6 (3.9)	4.7 (4.5)
SE	0.4	0.9
Median	4.0	4.0
Min, Max	0, 13	0, 14
Change from baseline		
n	77	26
Mean (SD)	0.0 (3.0)	0.0 (3.5)
SE	0.3	0.7
Median	0.0	0.0
Min, Max	-8, 7	-8, 10

Norfolk QoL-DN score = composite of 35 quality of life questions; lower scores indicate higher quality of life (range = -4 to 136). Nonmissing scores for items 27-33 imputed for patients who reported an impact due to COVID-19 pandemic. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

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Table 3.8
Norfolk Quality of Life - Diabetic Neuropathy (QoL-DN) Domain Scores: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Norfolk QoL-DN Domain: Small Fiber

Cardiac Subpopulation: No

Subgroup Visit	Vutrisiran (HELIOS-A) (N=82)	Patisiran (HELIOS-A) (N=28)
Month 18		
Actual Value		
n	77	25
Mean (SD)	4.8 (4.4)	4.8 (4.3)
SE	0.5	0.9
Median	4.0	4.0
Min, Max	0, 16	0, 14
Change from baseline		
n	76	25
Mean (SD)	0.2 (3.1)	0.0 (3.6)
SE	0.4	0.7
Median	0.0	0.0
Min, Max	-12, 7	-8, 5

Norfolk QoL-DN score = composite of 35 quality of life questions; lower scores indicate higher quality of life (range = -4 to 136). Nonmissing scores for items 27-33 imputed for patients who reported an impact due to COVID-19 pandemic. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

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Table 3.8
Norfolk Quality of Life - Diabetic Neuropathy (QoL-DN) Domain Scores: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Norfolk QoL-DN Domain: Small Fiber

Weight (kg): <65

Subgroup Visit	Vutrisiran (HELIOS-A) (N=46)	Patisiran (HELIOS-A) (N=15)
Baseline		
n	46	15
Mean (SD)	5.0 (4.5)	5.4 (5.1)
SE	0.7	1.3
Median	4.0	4.0
Min, Max	0, 16	0, 16
Month 9		
Actual Value		
n	44	15
Mean (SD)	5.2 (4.2)	4.7 (4.6)
SE	0.6	1.2
Median	5.0	4.0
Min, Max	0, 15	0, 15
Change from baseline		
n	44	15
Mean (SD)	0.3 (3.4)	-0.7 (2.5)
SE	0.5	0.6
Median	0.0	0.0
Min, Max	-8, 10	-8, 2

Norfolk QoL-DN score = composite of 35 quality of life questions; lower scores indicate higher quality of life (range = -4 to 136). Nonmissing scores for items 27-33 imputed for patients who reported an impact due to COVID-19 pandemic. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

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Table 3.8
Norfolk Quality of Life - Diabetic Neuropathy (QoL-DN) Domain Scores: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Norfolk QoL-DN Domain: Small Fiber

Weight (kg): <65

Subgroup Visit	Vutrisiran (HELIOS-A) (N=46)	Patisiran (HELIOS-A) (N=15)
Month 18		
Actual Value		
n	42	15
Mean (SD)	5.3 (4.8)	5.6 (5.5)
SE	0.7	1.4
Median	4.5	4.0
Min, Max	0, 16	0, 15
Change from baseline		
n	42	15
Mean (SD)	0.4 (3.4)	0.2 (3.3)
SE	0.5	0.9
Median	0.0	0.0
Min, Max	-10, 9	-8, 5

Norfolk QoL-DN score = composite of 35 quality of life questions; lower scores indicate higher quality of life (range = -4 to 136). Nonmissing scores for items 27-33 imputed for patients who reported an impact due to COVID-19 pandemic. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

Alnylam Pharmaceuticals Inc.
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Table 3.8
Norfolk Quality of Life - Diabetic Neuropathy (QoL-DN) Domain Scores: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Norfolk QoL-DN Domain: Small Fiber

Weight (kg): ≥65

Subgroup Visit	Vutrisiran (HELIOS-A) (N=76)	Patisiran (HELIOS-A) (N=27)
Baseline		
n	75	27
Mean (SD)	4.4 (4.0)	4.9 (4.3)
SE	0.5	0.8
Median	4.0	4.0
Min, Max	0, 14	0, 14
Month 9		
Actual Value		
n	72	25
Mean (SD)	4.2 (3.9)	5.2 (4.9)
SE	0.5	1.0
Median	3.0	5.0
Min, Max	0, 13	0, 14
Change from baseline		
n	71	25
Mean (SD)	0.0 (2.8)	0.2 (3.8)
SE	0.3	0.8
Median	0.0	0.0
Min, Max	-8, 7	-8, 10

Norfolk QoL-DN score = composite of 35 quality of life questions; lower scores indicate higher quality of life (range = -4 to 136). Nonmissing scores for items 27-33 imputed for patients who reported an impact due to COVID-19 pandemic. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

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Table 3.8
Norfolk Quality of Life - Diabetic Neuropathy (QoL-DN) Domain Scores: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Norfolk QoL-DN Domain: Small Fiber

Weight (kg): ≥65

Subgroup Visit	Vutrisiran (HELIOS-A) (N=76)	Patisiran (HELIOS-A) (N=27)
Month 18		
Actual Value		
n	72	23
Mean (SD)	4.8 (4.3)	4.8 (3.9)
SE	0.5	0.8
Median	4.0	6.0
Min, Max	0, 16	0, 12
Change from baseline		
n	71	23
Mean (SD)	0.6 (3.2)	0.0 (3.5)
SE	0.4	0.7
Median	0.0	0.0
Min, Max	-12, 9	-8, 7

Norfolk QoL-DN score = composite of 35 quality of life questions; lower scores indicate higher quality of life (range = -4 to 136). Nonmissing scores for items 27-33 imputed for patients who reported an impact due to COVID-19 pandemic. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

Norfolk-QoL-DN – Domäne Autonome Funktionen

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Table 3.5
Norfolk Quality of Life - Diabetic Neuropathy (QoL-DN) Domain Scores: Change from Baseline to Month 18, MMRM Model
Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A) Subgroup Analysis
mITT Population

Norfolk QoL-DN Domain: Autonomic

Subgroup Visit	LS Mean (95% CI) Vutrisiran (HELIOS-A) (N=122)	LS Mean (95% CI) Patisiran (HELIOS-A) (N=42)	LS Mean Difference (Vutrisiran-Patisiran) (95% CI), p-value	Standardized Effect Size (95% CI)
Age (years)				
<65	74	30		
Month 9	-0.30 (-0.65, 0.05)	-0.18 (-0.74, 0.38)	-0.12 (-0.78, 0.54), 0.7235	-0.07 (-0.49, 0.35)
Month 18	-0.37 (-0.74, 0.00)	-0.27 (-0.87, 0.33)	-0.10 (-0.81, 0.60), 0.7732	-0.06 (-0.49, 0.37)
≥65	43	10		
Month 9	-0.85 (-1.30, -0.41)	-0.63 (-1.53, 0.27)	-0.22 (-1.23, 0.78), 0.6637	-0.18 (-0.86, 0.50)
Month 18	-0.92 (-1.39, -0.46)	-0.72 (-1.65, 0.22)	-0.21 (-1.25, 0.84), 0.6969	-0.12 (-0.83, 0.60)
p-value of Treatment*Age	0.8572			

Norfolk QoL-DN score = composite of 35 quality of life questions; lower scores indicate higher quality of life (range = -4 to 136). Nonmissing scores for items 27-33 imputed for patients who reported an impact due to COVID-19 pandemic. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.
LS estimates and p-value derived from mixed-effects model for repeated measures (MMRM), controlling for categorical factors (treatment, visit), the subgroup variable, continuous covariate (baseline value), and interaction (treatment by visit, treatment by subgroup).
Standardized effect size (d) = LS mean difference/estimated pooled standard deviation with the small sample bias correction.

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

Alnylam Pharmaceuticals Inc.
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Table 3.5
Norfolk Quality of Life - Diabetic Neuropathy (QoL-DN) Domain Scores: Change from Baseline to Month 18, MMRM Model
Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A) Subgroup Analysis
mITT Population

Norfolk QoL-DN Domain: Autonomic

Subgroup Visit	LS Mean (95% CI) Vutrisiran (HELIOS-A) (N=122)	LS Mean (95% CI) Patisiran (HELIOS-A) (N=42)	LS Mean Difference (Vutrisiran-Patisiran) (95% CI), p-value	Standardized Effect Size (95% CI)
Sex				
Male	76	25		
Month 9	-0.53 (-0.88, -0.17)	-0.28 (-0.89, 0.33)	-0.25 (-0.96, 0.46), 0.4900	-0.15 (-0.60, 0.30)
Month 18	-0.59 (-0.97, -0.22)	-0.36 (-1.01, 0.29)	-0.24 (-0.98, 0.51), 0.5351	-0.14 (-0.61, 0.32)
Female	41	15		
Month 9	-0.45 (-0.91, 0.01)	-0.33 (-1.10, 0.44)	-0.12 (-1.01, 0.77), 0.7899	-0.08 (-0.66, 0.51)
Month 18	-0.52 (-0.99, -0.04)	-0.41 (-1.19, 0.38)	-0.11 (-1.02, 0.80), 0.8157	-0.06 (-0.64, 0.53)
p-value of Treatment*Sex	0.8115			

Norfolk QoL-DN score = composite of 35 quality of life questions; lower scores indicate higher quality of life (range = -4 to 136). Nonmissing scores for items 27-33 imputed for patients who reported an impact due to COVID-19 pandemic. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.
LS estimates and p-value derived from mixed-effects model for repeated measures (MMRM), controlling for categorical factors (treatment, visit), the subgroup variable, continuous covariate (baseline value), and interaction (treatment by visit, treatment by subgroup).
Standardized effect size (d) = LS mean difference/estimated pooled standard deviation with the small sample bias correction.

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

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Table 3.5
Norfolk Quality of Life - Diabetic Neuropathy (QoL-DN) Domain Scores: Change from Baseline to Month 18, MMRM Model
Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A) Subgroup Analysis
mITT Population

Norfolk QoL-DN Domain: Autonomic

Subgroup Visit	LS Mean (95% CI) Vutrisiran (HELIOS-A) (N=122)	LS Mean (95% CI) Patisiran (HELIOS-A) (N=42)	LS Mean Difference (Vutrisiran-Patisiran) (95% CI), p-value	Standardized Effect Size (95% CI)
Race				
White	82	28		
Month 9	-0.49 (-0.84, -0.15)	-0.48 (-1.06, 0.11)	-0.02 (-0.70, 0.66), 0.9572	-0.01 (-0.44, 0.41)
Month 18	-0.56 (-0.92, -0.20)	-0.55 (-1.17, 0.06)	-0.01 (-0.72, 0.70), 0.9822	-0.00 (-0.44, 0.43)
All Other Races	35	12		
Month 9	-0.52 (-1.01, -0.02)	0.11 (-0.73, 0.95)	-0.63 (-1.60, 0.35), 0.2075	-0.33 (-0.98, 0.32)
Month 18	-0.58 (-1.09, -0.08)	0.03 (-0.84, 0.90)	-0.62 (-1.62, 0.39), 0.2281	-0.38 (-1.06, 0.29)
p-value of Treatment*Race	0.2822			

Norfolk QoL-DN score = composite of 35 quality of life questions; lower scores indicate higher quality of life (range = -4 to 136). Nonmissing scores for items 27-33 imputed for patients who reported an impact due to COVID-19 pandemic. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.
LS estimates and p-value derived from mixed-effects model for repeated measures (MMRM), controlling for categorical factors (treatment, visit), the subgroup variable, continuous covariate (baseline value), and interaction (treatment by visit, treatment by subgroup).
Standardized effect size (d) = LS mean difference/estimated pooled standard deviation with the small sample bias correction.

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Table 3.5
Norfolk Quality of Life - Diabetic Neuropathy (QoL-DN) Domain Scores: Change from Baseline to Month 18, MMRM Model
Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A) Subgroup Analysis
mITT Population

Norfolk QoL-DN Domain: Autonomic

Subgroup Visit	LS Mean (95% CI) Vutrisiran (HELIOS-A) (N=122)	LS Mean (95% CI) Patisiran (HELIOS-A) (N=42)	LS Mean Difference (Vutrisiran-Patisiran) (95% CI), p-value	Standardized Effect Size (95% CI)
Region				
North America	26	8		
Month 9	-0.91 (-1.48, -0.34)	-0.09 (-1.10, 0.92)	-0.82 (-1.98, 0.34), 0.1630	-0.49 (-1.28, 0.29)
Month 18	-0.98 (-1.55, -0.40)	-0.16 (-1.19, 0.87)	-0.81 (-2.00, 0.37), 0.1756	-0.62 (-1.45, 0.22)
Western Europe	39	18		
Month 9	-0.49 (-0.95, -0.02)	-0.79 (-1.49, -0.10)	0.31 (-0.53, 1.14), 0.4720	0.22 (-0.33, 0.77)
Month 18	-0.55 (-1.02, -0.08)	-0.87 (-1.57, -0.16)	0.31 (-0.54, 1.16), 0.4674	0.22 (-0.33, 0.77)
Rest of World	52	14		
Month 9	-0.32 (-0.73, 0.09)	0.23 (-0.55, 1.01)	-0.55 (-1.42, 0.33), 0.2205	-0.30 (-0.89, 0.28)
Month 18	-0.38 (-0.80, 0.04)	0.16 (-0.64, 0.96)	-0.54 (-1.44, 0.36), 0.2410	-0.26 (-0.87, 0.34)
p-value of Treatment*Region	0.1736			

Norfolk QoL-DN score = composite of 35 quality of life questions; lower scores indicate higher quality of life (range = -4 to 136). Nonmissing scores for items 27-33 imputed for patients who reported an impact due to COVID-19 pandemic. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.
LS estimates and p-value derived from mixed-effects model for repeated measures (MMRM), controlling for categorical factors (treatment, visit), the subgroup variable, continuous covariate (baseline value), and interaction (treatment by visit, treatment by subgroup).
Standardized effect size (d) = LS mean difference/estimated pooled standard deviation with the small sample bias correction.

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Table 3.5
Norfolk Quality of Life - Diabetic Neuropathy (QoL-DN) Domain Scores: Change from Baseline to Month 18, MMRM Model
Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A) Subgroup Analysis
mITT Population

Norfolk QoL-DN Domain: Autonomic

Subgroup Visit	LS Mean (95% CI) Vutrisiran (HELIOS-A) (N=122)	LS Mean (95% CI) Patisiran (HELIOS-A) (N=42)	LS Mean Difference (Vutrisiran-Patisiran) (95% CI), p-value	Standardized Effect Size (95% CI)
Baseline NIS				
<50	76	27		
Month 9	-0.46 (-0.81, -0.11)	-0.47 (-1.07, 0.12)	0.01 (-0.68, 0.70), 0.9784	0.01 (-0.43, 0.44)
Month 18	-0.53 (-0.90, -0.16)	-0.55 (-1.17, 0.07)	0.02 (-0.71, 0.75), 0.9560	0.01 (-0.43, 0.45)
≥50	41	13		
Month 9	-0.57 (-1.03, -0.11)	0.06 (-0.75, 0.87)	-0.63 (-1.56, 0.31), 0.1858	-0.39 (-1.01, 0.23)
Month 18	-0.64 (-1.11, -0.16)	-0.02 (-0.86, 0.82)	-0.62 (-1.58, 0.35), 0.2080	-0.40 (-1.04, 0.25)
p-value of Treatment*Baseline NIS	0.2475			

Norfolk QoL-DN score = composite of 35 quality of life questions; lower scores indicate higher quality of life (range = -4 to 136). Nonmissing scores for items 27-33 imputed for patients who reported an impact due to COVID-19 pandemic. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.
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Table 3.5
Norfolk Quality of Life - Diabetic Neuropathy (QoL-DN) Domain Scores: Change from Baseline to Month 18, MMRM Model
Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A) Subgroup Analysis
mITT Population

Norfolk QoL-DN Domain: Autonomic

Subgroup Visit	LS Mean (95% CI) Vutrisiran (HELIOS-A) (N=122)	LS Mean (95% CI) Patisiran (HELIOS-A) (N=42)	LS Mean Difference (Vutrisiran-Patisiran) (95% CI), p-value	Standardized Effect Size (95% CI)
Previous Tetramer Stabilizer Use				
Yes	74	32		
Month 9	-0.42 (-0.78, -0.07)	-0.33 (-0.88, 0.23)	-0.10 (-0.75, 0.56), 0.7733	-0.06 (-0.47, 0.35)
Month 18	-0.49 (-0.86, -0.12)	-0.41 (-0.99, 0.18)	-0.08 (-0.78, 0.61), 0.8163	-0.05 (-0.47, 0.37)
No	43	8		
Month 9	-0.64 (-1.09, -0.18)	-0.18 (-1.20, 0.84)	-0.45 (-1.57, 0.66), 0.4232	-0.26 (-1.01, 0.48)
Month 18	-0.70 (-1.16, -0.24)	-0.26 (-1.31, 0.79)	-0.44 (-1.59, 0.71), 0.4497	-0.22 (-1.01, 0.57)
p-value of Treatment*Previous Tetramer Stabilizer Use	0.5656			

Norfolk QoL-DN score = composite of 35 quality of life questions; lower scores indicate higher quality of life (range = -4 to 136). Nonmissing scores for items 27-33 imputed for patients who reported an impact due to COVID-19 pandemic. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.
LS estimates and p-value derived from mixed-effects model for repeated measures (MMRM), controlling for categorical factors (treatment, visit), the subgroup variable, continuous covariate (baseline value), and interaction (treatment by visit, treatment by subgroup).
Standardized effect size (d) = LS mean difference/estimated pooled standard deviation with the small sample bias correction.

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Table 3.5
Norfolk Quality of Life - Diabetic Neuropathy (QoL-DN) Domain Scores: Change from Baseline to Month 18, MMRM Model
Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A) Subgroup Analysis
mITT Population

Norfolk QoL-DN Domain: Autonomic

Subgroup Visit	LS Mean (95% CI) Vutrisiran (HELIOS-A) (N=122)	LS Mean (95% CI) Patisiran (HELIOS-A) (N=42)	LS Mean Difference (Vutrisiran-Patisiran) (95% CI), p-value	Standardized Effect Size (95% CI)
Genotype				
V30M	52	20		
Month 9	-0.71 (-1.12, -0.31)	-0.76 (-1.42, -0.10)	0.05 (-0.72, 0.82), 0.9035	0.03 (-0.48, 0.55)
Month 18	-0.78 (-1.20, -0.35)	-0.83 (-1.52, -0.13)	0.05 (-0.76, 0.86), 0.9064	0.02 (-0.49, 0.54)
non-V30M	65	20		
Month 9	-0.33 (-0.70, 0.04)	0.16 (-0.50, 0.81)	-0.49 (-1.24, 0.26), 0.2019	-0.29 (-0.78, 0.21)
Month 18	-0.40 (-0.79, -0.00)	0.09 (-0.62, 0.80)	-0.49 (-1.30, 0.32), 0.2357	-0.32 (-0.84, 0.20)
p-value of Treatment*Genotype	0.2921			

Norfolk QoL-DN score = composite of 35 quality of life questions; lower scores indicate higher quality of life (range = -4 to 136). Nonmissing scores for items 27-33 imputed for patients who reported an impact due to COVID-19 pandemic. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.
LS estimates and p-value derived from mixed-effects model for repeated measures (MMRM), controlling for categorical factors (treatment, visit), the subgroup variable, continuous covariate (baseline value), and interaction (treatment by visit, treatment by subgroup).
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Table 3.5
Norfolk Quality of Life - Diabetic Neuropathy (QoL-DN) Domain Scores: Change from Baseline to Month 18, MMRM Model
Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A) Subgroup Analysis
mITT Population

Norfolk QoL-DN Domain: Autonomic

Subgroup Visit	LS Mean (95% CI) Vutrisiran (HELIOS-A) (N=122)	LS Mean (95% CI) Patisiran (HELIOS-A) (N=42)	LS Mean Difference (Vutrisiran-Patisiran) (95% CI), p-value	Standardized Effect Size (95% CI)
FAP Stage				
I	82	30		
Month 9	-0.48 (-0.82, -0.14)	-0.50 (-1.07, 0.06)	0.02 (-0.64, 0.69), 0.9408	0.02 (-0.40, 0.43)
Month 18	-0.55 (-0.90, -0.19)	-0.57 (-1.16, 0.03)	0.02 (-0.68, 0.72), 0.9565	0.01 (-0.41, 0.43)
II&III	35	10		
Month 9	-0.55 (-1.04, -0.06)	0.31 (-0.61, 1.23)	-0.86 (-1.90, 0.18), 0.1048	-0.52 (-1.22, 0.18)
Month 18	-0.62 (-1.12, -0.11)	0.25 (-0.71, 1.21)	-0.87 (-1.95, 0.22), 0.1174	-0.63 (-1.40, 0.14)
p-value of Treatment*FAP Stage	0.1364			

Norfolk QoL-DN score = composite of 35 quality of life questions; lower scores indicate higher quality of life (range = -4 to 136). Nonmissing scores for items 27-33 imputed for patients who reported an impact due to COVID-19 pandemic. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.
LS estimates and p-value derived from mixed-effects model for repeated measures (MMRM), controlling for categorical factors (treatment, visit), the subgroup variable, continuous covariate (baseline value), and interaction (treatment by visit, treatment by subgroup).
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Table 3.5
Norfolk Quality of Life - Diabetic Neuropathy (QoL-DN) Domain Scores: Change from Baseline to Month 18, MMRM Model
Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A) Subgroup Analysis
mITT Population

Norfolk QoL-DN Domain: Autonomic

Subgroup Visit	LS Mean (95% CI) Vutrisiran (HELIOS-A) (N=122)	LS Mean (95% CI) Patisiran (HELIOS-A) (N=42)	LS Mean Difference (Vutrisiran-Patisiran) (95% CI), p-value	Standardized Effect Size (95% CI)
Cardiac Subpopulation				
Yes	38	14		
Month 9	-0.41 (-0.88, 0.06)	-0.00 (-0.79, 0.78)	-0.40 (-1.32, 0.51), 0.3838	-0.24 (-0.85, 0.36)
Month 18	-0.48 (-0.96, 0.01)	-0.08 (-0.90, 0.73)	-0.39 (-1.34, 0.55), 0.4139	-0.25 (-0.87, 0.38)
No	79	26		
Month 9	-0.55 (-0.89, -0.20)	-0.46 (-1.06, 0.14)	-0.09 (-0.79, 0.61), 0.8030	-0.06 (-0.50, 0.39)
Month 18	-0.61 (-0.98, -0.25)	-0.54 (-1.17, 0.10)	-0.08 (-0.81, 0.66), 0.8370	-0.04 (-0.49, 0.41)
p-value of Treatment*Cardiac Subpopulation	0.5607			

Norfolk QoL-DN score = composite of 35 quality of life questions; lower scores indicate higher quality of life (range = -4 to 136). Nonmissing scores for items 27-33 imputed for patients who reported an impact due to COVID-19 pandemic. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.
LS estimates and p-value derived from mixed-effects model for repeated measures (MMRM), controlling for categorical factors (treatment, visit), the subgroup variable, continuous covariate (baseline value), and interaction (treatment by visit, treatment by subgroup).
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Table 3.5
Norfolk Quality of Life - Diabetic Neuropathy (QoL-DN) Domain Scores: Change from Baseline to Month 18, MMRM Model
Vutrisiran (HELIOS-A) vs. Patisiran (HELIOS-A) Subgroup Analysis
mITT Population

Norfolk QoL-DN Domain: Autonomic

Subgroup Visit	LS Mean (95% CI) Vutrisiran (HELIOS-A) (N=122)	LS Mean (95% CI) Patisiran (HELIOS-A) (N=42)	LS Mean Difference (Vutrisiran-Patisiran) (95% CI), p-value	Standardized Effect Size (95% CI)
Weight (kg)				
<65	44	15		
Month 9	-0.31 (-0.76, 0.13)	-0.05 (-0.82, 0.73)	-0.27 (-1.15, 0.62), 0.5530	-0.14 (-0.72, 0.44)
Month 18	-0.38 (-0.84, 0.08)	-0.13 (-0.92, 0.66)	-0.24 (-1.15, 0.66), 0.5959	-0.14 (-0.72, 0.44)
≥65	73	25		
Month 9	-0.62 (-0.98, -0.26)	-0.44 (-1.05, 0.17)	-0.18 (-0.89, 0.53), 0.6176	-0.12 (-0.58, 0.33)
Month 18	-0.68 (-1.06, -0.31)	-0.53 (-1.17, 0.12)	-0.16 (-0.90, 0.59), 0.6787	-0.09 (-0.56, 0.37)
p-value of Treatment*Weight	0.8702			

Norfolk QoL-DN score = composite of 35 quality of life questions; lower scores indicate higher quality of life (range = -4 to 136). Nonmissing scores for items 27-33 imputed for patients who reported an impact due to COVID-19 pandemic. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.
LS estimates and p-value derived from mixed-effects model for repeated measures (MMRM), controlling for categorical factors (treatment, visit), the subgroup variable, continuous covariate (baseline value), and interaction (treatment by visit, treatment by subgroup).
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Table 3.8
Norfolk Quality of Life - Diabetic Neuropathy (QoL-DN) Domain Scores: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Norfolk QoL-DN Domain: Autonomic

Age (years): <65

Subgroup Visit	Vutrisiran (HELIOS-A) (N=76)	Patisiran (HELIOS-A) (N=31)
Baseline		
n	75	31
Mean (SD)	3.1 (3.1)	3.3 (2.8)
SE	0.4	0.5
Median	2.0	3.0
Min, Max	0, 12	0, 10
Month 9		
Actual Value		
n	74	30
Mean (SD)	2.7 (2.4)	2.8 (2.4)
SE	0.3	0.4
Median	2.5	3.0
Min, Max	0, 10	0, 9
Change from baseline		
n	73	30
Mean (SD)	-0.3 (2.4)	-0.6 (1.4)
SE	0.3	0.3
Median	0.0	-1.0
Min, Max	-7, 4	-4, 3

Norfolk QoL-DN score = composite of 35 quality of life questions; lower scores indicate higher quality of life (range = -4 to 136). Nonmissing scores for items 27-33 imputed for patients who reported an impact due to COVID-19 pandemic. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 3.8
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mITT Population

Norfolk QoL-DN Domain: Autonomic

Age (years): <65

Subgroup Visit	Vutrisiran (HELIOS-A) (N=76)	Patisiran (HELIOS-A) (N=31)
Month 18		
Actual Value		
n	74	29
Mean (SD)	2.3 (2.0)	2.8 (2.5)
SE	0.2	0.5
Median	2.0	2.0
Min, Max	0, 9	0, 8
Change from baseline		
n	73	29
Mean (SD)	-0.7 (2.5)	-0.4 (1.3)
SE	0.3	0.2
Median	0.0	0.0
Min, Max	-9, 5	-3, 2

Norfolk QoL-DN score = composite of 35 quality of life questions; lower scores indicate higher quality of life (range = -4 to 136). Nonmissing scores for items 27-33 imputed for patients who reported an impact due to COVID-19 pandemic. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 3.8
Norfolk Quality of Life - Diabetic Neuropathy (QoL-DN) Domain Scores: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Norfolk QoL-DN Domain: Autonomic

Age (years): ≥65

Subgroup Visit	Vutrisiran (HELIOS-A) (N=46)	Patisiran (HELIOS-A) (N=11)
Baseline		
n	46	11
Mean (SD)	2.1 (2.3)	2.0 (2.5)
SE	0.3	0.8
Median	1.5	2.0
Min, Max	0, 8	0, 8
Month 9		
Actual Value		
n	42	10
Mean (SD)	1.3 (1.5)	2.1 (1.5)
SE	0.2	0.5
Median	1.0	2.5
Min, Max	0, 5	0, 4
Change from baseline		
n	42	10
Mean (SD)	-0.7 (1.9)	-0.1 (2.0)
SE	0.3	0.6
Median	0.0	-0.5
Min, Max	-6, 3	-4, 3

Norfolk QoL-DN score = composite of 35 quality of life questions; lower scores indicate higher quality of life (range = -4 to 136). Nonmissing scores for items 27-33 imputed for patients who reported an impact due to COVID-19 pandemic. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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mITT Population

Norfolk QoL-DN Domain: Autonomic

Age (years): ≥65

Subgroup Visit	Vutrisiran (HELIOS-A) (N=46)	Patisiran (HELIOS-A) (N=11)
Month 18		
Actual Value		
n	40	9
Mean (SD)	1.9 (2.0)	1.4 (1.6)
SE	0.3	0.5
Median	2.0	1.0
Min, Max	0, 9	0, 4
Change from baseline		
n	40	9
Mean (SD)	-0.4 (2.4)	-1.0 (1.7)
SE	0.4	0.6
Median	0.0	-1.0
Min, Max	-5, 9	-4, 1

Norfolk QoL-DN score = composite of 35 quality of life questions; lower scores indicate higher quality of life (range = -4 to 136). Nonmissing scores for items 27-33 imputed for patients who reported an impact due to COVID-19 pandemic. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 3.8
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mITT Population

Norfolk QoL-DN Domain: Autonomic

Sex: Male

Subgroup Visit	Vutrisiran (HELIOS-A) (N=79)	Patisiran (HELIOS-A) (N=27)
Baseline		
n	78	27
Mean (SD)	2.2 (2.4)	2.5 (2.7)
SE	0.3	0.5
Median	1.0	2.0
Min, Max	0, 9	0, 9
Month 9		
Actual Value		
n	76	25
Mean (SD)	1.9 (2.0)	2.5 (2.3)
SE	0.2	0.5
Median	1.0	2.0
Min, Max	0, 8	0, 9
Change from baseline		
n	75	25
Mean (SD)	-0.3 (2.2)	-0.2 (1.5)
SE	0.3	0.3
Median	0.0	-1.0
Min, Max	-7, 4	-2, 3

Norfolk QoL-DN score = composite of 35 quality of life questions; lower scores indicate higher quality of life (range = -4 to 136). Nonmissing scores for items 27-33 imputed for patients who reported an impact due to COVID-19 pandemic. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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mITT Population

Norfolk QoL-DN Domain: Autonomic

Sex: Male

Subgroup Visit	Vutrisiran (HELIOS-A) (N=79)	Patisiran (HELIOS-A) (N=27)
Month 18		
Actual Value		
n	74	23
Mean (SD)	2.0 (1.9)	2.1 (2.5)
SE	0.2	0.5
Median	2.0	1.0
Min, Max	0, 9	0, 8
Change from baseline		
n	73	23
Mean (SD)	-0.3 (2.2)	-0.4 (1.1)
SE	0.3	0.2
Median	0.0	0.0
Min, Max	-6, 5	-2, 2

Norfolk QoL-DN score = composite of 35 quality of life questions; lower scores indicate higher quality of life (range = -4 to 136). Nonmissing scores for items 27-33 imputed for patients who reported an impact due to COVID-19 pandemic. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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mITT Population

Norfolk QoL-DN Domain: Autonomic

Sex: Female

Subgroup Visit	Vutrisiran (HELIOS-A) (N=43)	Patisiran (HELIOS-A) (N=15)
Baseline		
n	43	15
Mean (SD)	3.6 (3.4)	3.9 (2.7)
SE	0.5	0.7
Median	2.0	4.0
Min, Max	0, 12	1, 10
Month 9		
Actual Value		
n	40	15
Mean (SD)	2.8 (2.5)	2.9 (2.0)
SE	0.4	0.5
Median	2.0	3.0
Min, Max	0, 10	0, 6
Change from baseline		
n	40	15
Mean (SD)	-0.7 (2.2)	-1.0 (1.6)
SE	0.3	0.4
Median	0.0	-1.0
Min, Max	-6, 4	-4, 1

Norfolk QoL-DN score = composite of 35 quality of life questions; lower scores indicate higher quality of life (range = -4 to 136). Nonmissing scores for items 27-33 imputed for patients who reported an impact due to COVID-19 pandemic. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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mITT Population

Norfolk QoL-DN Domain: Autonomic

Sex: Female

Subgroup Visit	Vutrisiran (HELIOS-A) (N=43)	Patisiran (HELIOS-A) (N=15)
Month 18		
Actual Value		
n	40	15
Mean (SD)	2.5 (2.1)	3.1 (2.1)
SE	0.3	0.5
Median	2.0	2.0
Min, Max	0, 9	0, 8
Change from baseline		
n	40	15
Mean (SD)	-1.0 (2.9)	-0.8 (1.8)
SE	0.5	0.5
Median	-0.5	-1.0
Min, Max	-9, 9	-4, 2

Norfolk QoL-DN score = composite of 35 quality of life questions; lower scores indicate higher quality of life (range = -4 to 136). Nonmissing scores for items 27-33 imputed for patients who reported an impact due to COVID-19 pandemic. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

Alnylam Pharmaceuticals Inc.
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Table 3.8
Norfolk Quality of Life - Diabetic Neuropathy (QoL-DN) Domain Scores: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Norfolk QoL-DN Domain: Autonomic

Race: White

Subgroup Visit	Vutrisiran (HELIOS-A) (N=86)	Patisiran (HELIOS-A) (N=29)
Baseline		
n	85	29
Mean (SD)	2.6 (2.7)	3.2 (2.7)
SE	0.3	0.5
Median	2.0	2.0
Min, Max	0, 11	0, 10
Month 9		
Actual Value		
n	82	28
Mean (SD)	2.1 (2.2)	2.6 (2.3)
SE	0.2	0.4
Median	1.5	3.0
Min, Max	0, 10	0, 9
Change from baseline		
n	81	28
Mean (SD)	-0.5 (2.0)	-0.7 (1.4)
SE	0.2	0.3
Median	0.0	-1.0
Min, Max	-6, 4	-4, 3

Norfolk QoL-DN score = composite of 35 quality of life questions; lower scores indicate higher quality of life (range = -4 to 136). Nonmissing scores for items 27-33 imputed for patients who reported an impact due to COVID-19 pandemic. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

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Table 3.8
Norfolk Quality of Life - Diabetic Neuropathy (QoL-DN) Domain Scores: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Norfolk QoL-DN Domain: Autonomic

Race: White

Subgroup Visit	Vutrisiran (HELIOS-A) (N=86)	Patisiran (HELIOS-A) (N=29)
Month 18		
Actual Value		
n	81	27
Mean (SD)	2.2 (2.2)	2.3 (2.2)
SE	0.2	0.4
Median	2.0	2.0
Min, Max	0, 9	0, 8
Change from baseline		
n	80	27
Mean (SD)	-0.5 (2.5)	-0.8 (1.4)
SE	0.3	0.3
Median	0.0	-1.0
Min, Max	-9, 9	-4, 2

Norfolk QoL-DN score = composite of 35 quality of life questions; lower scores indicate higher quality of life (range = -4 to 136). Nonmissing scores for items 27-33 imputed for patients who reported an impact due to COVID-19 pandemic. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 3.8
Norfolk Quality of Life - Diabetic Neuropathy (QoL-DN) Domain Scores: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Norfolk QoL-DN Domain: Autonomic

Race: All Other Races

Subgroup Visit	Vutrisiran (HELIOS-A) (N=36)	Patisiran (HELIOS-A) (N=13)
Baseline		
n	36	13
Mean (SD)	2.9 (3.1)	2.5 (2.8)
SE	0.5	0.8
Median	2.0	1.0
Min, Max	0, 12	0, 8
Month 9		
Actual Value		
n	34	12
Mean (SD)	2.3 (2.3)	2.8 (2.0)
SE	0.4	0.6
Median	2.0	2.5
Min, Max	0, 8	0, 6
Change from baseline		
n	34	12
Mean (SD)	-0.3 (2.6)	0.1 (1.7)
SE	0.4	0.5
Median	0.0	0.0
Min, Max	-7, 4	-2, 3

Norfolk QoL-DN score = composite of 35 quality of life questions; lower scores indicate higher quality of life (range = -4 to 136). Nonmissing scores for items 27-33 imputed for patients who reported an impact due to COVID-19 pandemic. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 3.8
Norfolk Quality of Life - Diabetic Neuropathy (QoL-DN) Domain Scores: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Norfolk QoL-DN Domain: Autonomic

Race: All Other Races

Subgroup Visit	Vutrisiran (HELIOS-A) (N=36)	Patisiran (HELIOS-A) (N=13)
Month 18		
Actual Value		
n	33	11
Mean (SD)	2.0 (1.6)	2.9 (2.8)
SE	0.3	0.8
Median	2.0	2.0
Min, Max	0, 5	0, 8
Change from baseline		
n	33	11
Mean (SD)	-0.8 (2.4)	0.0 (1.3)
SE	0.4	0.4
Median	0.0	0.0
Min, Max	-8, 3	-3, 2

Norfolk QoL-DN score = composite of 35 quality of life questions; lower scores indicate higher quality of life (range = -4 to 136). Nonmissing scores for items 27-33 imputed for patients who reported an impact due to COVID-19 pandemic. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 3.8
Norfolk Quality of Life - Diabetic Neuropathy (QoL-DN) Domain Scores: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Norfolk QoL-DN Domain: Autonomic

Region: North America

Subgroup Visit	Vutrisiran (HELIOS-A) (N=27)	Patisiran (HELIOS-A) (N=8)
Baseline		
n	26	8
Mean (SD)	1.9 (2.5)	3.0 (3.3)
SE	0.5	1.2
Median	1.0	2.0
Min, Max	0, 8	0, 10
Month 9		
Actual Value		
n	25	8
Mean (SD)	1.4 (2.1)	3.0 (2.0)
SE	0.4	0.7
Median	0.0	3.0
Min, Max	0, 8	0, 6
Change from baseline		
n	24	8
Mean (SD)	-0.4 (2.2)	0.0 (2.1)
SE	0.5	0.8
Median	0.0	0.0
Min, Max	-7, 4	-4, 3

Norfolk QoL-DN score = composite of 35 quality of life questions; lower scores indicate higher quality of life (range = -4 to 136). Nonmissing scores for items 27-33 imputed for patients who reported an impact due to COVID-19 pandemic. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

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Table 3.8
Norfolk Quality of Life - Diabetic Neuropathy (QoL-DN) Domain Scores: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Norfolk QoL-DN Domain: Autonomic

Region: North America

Subgroup Visit	Vutrisiran (HELIOS-A) (N=27)	Patisiran (HELIOS-A) (N=8)
Month 18		
Actual Value		
n	25	7
Mean (SD)	1.2 (1.3)	2.6 (2.9)
SE	0.3	1.1
Median	1.0	2.0
Min, Max	0, 5	0, 8
Change from baseline		
n	24	7
Mean (SD)	-0.8 (2.1)	-0.9 (1.2)
SE	0.4	0.5
Median	0.0	-1.0
Min, Max	-6, 2	-2, 1

Norfolk QoL-DN score = composite of 35 quality of life questions; lower scores indicate higher quality of life (range = -4 to 136). Nonmissing scores for items 27-33 imputed for patients who reported an impact due to COVID-19 pandemic. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

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Table 3.8
Norfolk Quality of Life - Diabetic Neuropathy (QoL-DN) Domain Scores: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Norfolk QoL-DN Domain: Autonomic

Region: Western Europe

Subgroup Visit	Vutrisiran (HELIOS-A) (N=42)	Patisiran (HELIOS-A) (N=20)
Baseline		
n	42	20
Mean (SD)	2.6 (2.6)	2.7 (2.4)
SE	0.4	0.5
Median	2.0	2.0
Min, Max	0, 10	0, 8
Month 9		
Actual Value		
n	39	18
Mean (SD)	2.3 (2.0)	2.1 (1.7)
SE	0.3	0.4
Median	2.0	2.5
Min, Max	0, 7	0, 5
Change from baseline		
n	39	18
Mean (SD)	-0.3 (2.1)	-0.9 (1.1)
SE	0.3	0.3
Median	0.0	-1.0
Min, Max	-6, 4	-4, 1

Norfolk QoL-DN score = composite of 35 quality of life questions; lower scores indicate higher quality of life (range = -4 to 136). Nonmissing scores for items 27-33 imputed for patients who reported an impact due to COVID-19 pandemic. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 3.8
Norfolk Quality of Life - Diabetic Neuropathy (QoL-DN) Domain Scores: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Norfolk QoL-DN Domain: Autonomic

Region: Western Europe

Subgroup Visit	Vutrisiran (HELIOS-A) (N=42)	Patisiran (HELIOS-A) (N=20)
Month 18		
Actual Value		
n	39	18
Mean (SD)	2.1 (2.0)	2.1 (2.0)
SE	0.3	0.5
Median	2.0	2.0
Min, Max	0, 8	0, 6
Change from baseline		
n	39	18
Mean (SD)	-0.6 (2.1)	-0.9 (1.3)
SE	0.3	0.3
Median	0.0	-1.0
Min, Max	-6, 3	-4, 1

Norfolk QoL-DN score = composite of 35 quality of life questions; lower scores indicate higher quality of life (range = -4 to 136). Nonmissing scores for items 27-33 imputed for patients who reported an impact due to COVID-19 pandemic. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 3.8
Norfolk Quality of Life - Diabetic Neuropathy (QoL-DN) Domain Scores: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Norfolk QoL-DN Domain: Autonomic

Region: Rest of World

Subgroup Visit	Vutrisiran (HELIOS-A) (N=53)	Patisiran (HELIOS-A) (N=14)
Baseline		
n	53	14
Mean (SD)	3.2 (3.1)	3.4 (3.0)
SE	0.4	0.8
Median	2.0	2.0
Min, Max	0, 12	0, 9
Month 9		
Actual Value		
n	52	14
Mean (SD)	2.4 (2.4)	3.2 (2.8)
SE	0.3	0.7
Median	2.0	3.0
Min, Max	0, 10	0, 9
Change from baseline		
n	52	14
Mean (SD)	-0.6 (2.3)	-0.1 (1.6)
SE	0.3	0.4
Median	0.0	0.0
Min, Max	-6, 4	-2, 3

Norfolk QoL-DN score = composite of 35 quality of life questions; lower scores indicate higher quality of life (range = -4 to 136). Nonmissing scores for items 27-33 imputed for patients who reported an impact due to COVID-19 pandemic. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 3.8
Norfolk Quality of Life - Diabetic Neuropathy (QoL-DN) Domain Scores: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Norfolk QoL-DN Domain: Autonomic

Region: Rest of World

Subgroup Visit	Vutrisiran (HELIOS-A) (N=53)	Patisiran (HELIOS-A) (N=14)
Month 18		
Actual Value		
n	50	13
Mean (SD)	2.7 (2.2)	3.0 (2.6)
SE	0.3	0.7
Median	2.5	3.0
Min, Max	0, 9	0, 8
Change from baseline		
n	50	13
Mean (SD)	-0.4 (2.9)	0.1 (1.6)
SE	0.4	0.4
Median	0.0	0.0
Min, Max	-9, 9	-3, 2

Norfolk QoL-DN score = composite of 35 quality of life questions; lower scores indicate higher quality of life (range = -4 to 136). Nonmissing scores for items 27-33 imputed for patients who reported an impact due to COVID-19 pandemic. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 3.8
Norfolk Quality of Life - Diabetic Neuropathy (QoL-DN) Domain Scores: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Norfolk QoL-DN Domain: Autonomic

Baseline NIS: <50

Subgroup Visit	Vutrisiran (HELIOS-A) (N=78)	Patisiran (HELIOS-A) (N=27)
Baseline		
n	77	27
Mean (SD)	2.6 (2.8)	3.3 (2.7)
SE	0.3	0.5
Median	2.0	2.0
Min, Max	0, 12	0, 10
Month 9		
Actual Value		
n	77	27
Mean (SD)	2.2 (2.3)	2.5 (2.0)
SE	0.3	0.4
Median	2.0	3.0
Min, Max	0, 10	0, 6
Change from baseline		
n	76	27
Mean (SD)	-0.3 (2.2)	-0.8 (1.4)
SE	0.3	0.3
Median	0.0	-1.0
Min, Max	-7, 4	-4, 3

Norfolk QoL-DN score = composite of 35 quality of life questions; lower scores indicate higher quality of life (range = -4 to 136). Nonmissing scores for items 27-33 imputed for patients who reported an impact due to COVID-19 pandemic. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 3.8
Norfolk Quality of Life - Diabetic Neuropathy (QoL-DN) Domain Scores: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Norfolk QoL-DN Domain: Autonomic

Baseline NIS: <50

Subgroup Visit	Vutrisiran (HELIOS-A) (N=78)	Patisiran (HELIOS-A) (N=27)
Month 18		
Actual Value		
n	75	26
Mean (SD)	2.1 (2.0)	2.6 (2.7)
SE	0.2	0.5
Median	2.0	2.0
Min, Max	0, 9	0, 8
Change from baseline		
n	74	26
Mean (SD)	-0.5 (2.5)	-0.8 (1.2)
SE	0.3	0.2
Median	0.0	-1.0
Min, Max	-9, 9	-3, 2

Norfolk QoL-DN score = composite of 35 quality of life questions; lower scores indicate higher quality of life (range = -4 to 136). Nonmissing scores for items 27-33 imputed for patients who reported an impact due to COVID-19 pandemic. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 3.8
Norfolk Quality of Life - Diabetic Neuropathy (QoL-DN) Domain Scores: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Norfolk QoL-DN Domain: Autonomic

Baseline NIS: ≥50

Subgroup Visit	Vutrisiran (HELIOS-A) (N=44)	Patisiran (HELIOS-A) (N=15)
Baseline		
n	44	15
Mean (SD)	2.8 (2.9)	2.4 (2.8)
SE	0.4	0.7
Median	2.0	1.0
Min, Max	0, 11	0, 9
Month 9		
Actual Value		
n	39	13
Mean (SD)	2.2 (2.2)	2.9 (2.6)
SE	0.3	0.7
Median	2.0	3.0
Min, Max	0, 7	0, 9
Change from baseline		
n	39	13
Mean (SD)	-0.7 (2.2)	0.2 (1.7)
SE	0.4	0.5
Median	0.0	0.0
Min, Max	-6, 4	-4, 3

Norfolk QoL-DN score = composite of 35 quality of life questions; lower scores indicate higher quality of life (range = -4 to 136). Nonmissing scores for items 27-33 imputed for patients who reported an impact due to COVID-19 pandemic. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 3.8
Norfolk Quality of Life - Diabetic Neuropathy (QoL-DN) Domain Scores: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Norfolk QoL-DN Domain: Autonomic

Baseline NIS: ≥50

Subgroup Visit	Vutrisiran (HELIOS-A) (N=44)	Patisiran (HELIOS-A) (N=15)
Month 18		
Actual Value		
n	39	12
Mean (SD)	2.3 (2.0)	2.3 (1.4)
SE	0.3	0.4
Median	2.0	2.5
Min, Max	0, 9	0, 4
Change from baseline		
n	39	12
Mean (SD)	-0.7 (2.4)	0.0 (1.8)
SE	0.4	0.5
Median	0.0	0.5
Min, Max	-8, 3	-4, 2

Norfolk QoL-DN score = composite of 35 quality of life questions; lower scores indicate higher quality of life (range = -4 to 136). Nonmissing scores for items 27-33 imputed for patients who reported an impact due to COVID-19 pandemic. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 3.8
Norfolk Quality of Life - Diabetic Neuropathy (QoL-DN) Domain Scores: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Norfolk QoL-DN Domain: Autonomic

Previous Tetramer Stabilizer Use: Yes

Subgroup Visit	Vutrisiran (HELIOS-A) (N=75)	Patisiran (HELIOS-A) (N=33)
Baseline		
n	75	33
Mean (SD)	2.7 (2.7)	3.0 (2.5)
SE	0.3	0.4
Median	2.0	2.0
Min, Max	0, 11	0, 9
Month 9		
Actual Value		
n	74	32
Mean (SD)	2.4 (2.2)	2.7 (2.2)
SE	0.3	0.4
Median	2.0	3.0
Min, Max	0, 10	0, 9
Change from baseline		
n	74	32
Mean (SD)	-0.3 (2.1)	-0.5 (1.3)
SE	0.2	0.2
Median	0.0	-0.5
Min, Max	-6, 4	-4, 3

Norfolk QoL-DN score = composite of 35 quality of life questions; lower scores indicate higher quality of life (range = -4 to 136). Nonmissing scores for items 27-33 imputed for patients who reported an impact due to COVID-19 pandemic. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 3.8
Norfolk Quality of Life - Diabetic Neuropathy (QoL-DN) Domain Scores: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Norfolk QoL-DN Domain: Autonomic

Previous Tetramer Stabilizer Use: Yes

Subgroup Visit	Vutrisiran (HELIOS-A) (N=75)	Patisiran (HELIOS-A) (N=33)
Month 18		
Actual Value		
n	71	31
Mean (SD)	2.2 (2.0)	2.4 (2.0)
SE	0.2	0.4
Median	2.0	2.0
Min, Max	0, 9	0, 8
Change from baseline		
n	71	31
Mean (SD)	-0.6 (2.2)	-0.6 (1.4)
SE	0.3	0.3
Median	0.0	0.0
Min, Max	-9, 5	-4, 2

Norfolk QoL-DN score = composite of 35 quality of life questions; lower scores indicate higher quality of life (range = -4 to 136). Nonmissing scores for items 27-33 imputed for patients who reported an impact due to COVID-19 pandemic. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 3.8
Norfolk Quality of Life - Diabetic Neuropathy (QoL-DN) Domain Scores: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Norfolk QoL-DN Domain: Autonomic

Previous Tetramer Stabilizer Use: No

Subgroup Visit	Vutrisiran (HELIOS-A) (N=47)	Patisiran (HELIOS-A) (N=9)
Baseline		
n	46	9
Mean (SD)	2.7 (3.1)	2.8 (3.7)
SE	0.5	1.2
Median	2.0	2.0
Min, Max	0, 12	0, 10
Month 9		
Actual Value		
n	42	8
Mean (SD)	1.8 (2.1)	2.6 (2.4)
SE	0.3	0.8
Median	1.0	2.5
Min, Max	0, 8	0, 6
Change from baseline		
n	41	8
Mean (SD)	-0.7 (2.4)	-0.5 (2.3)
SE	0.4	0.8
Median	0.0	-1.0
Min, Max	-7, 4	-4, 3

Norfolk QoL-DN score = composite of 35 quality of life questions; lower scores indicate higher quality of life (range = -4 to 136). Nonmissing scores for items 27-33 imputed for patients who reported an impact due to COVID-19 pandemic. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 3.8
Norfolk Quality of Life - Diabetic Neuropathy (QoL-DN) Domain Scores: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Norfolk QoL-DN Domain: Autonomic

Previous Tetramer Stabilizer Use: No

Subgroup Visit	Vutrisiran (HELIOS-A) (N=47)	Patisiran (HELIOS-A) (N=9)
Month 18		
Actual Value		
n	43	7
Mean (SD)	2.1 (2.0)	3.0 (3.7)
SE	0.3	1.4
Median	2.0	1.0
Min, Max	0, 9	0, 8
Change from baseline		
n	42	7
Mean (SD)	-0.5 (2.8)	-0.6 (1.4)
SE	0.4	0.5
Median	0.0	-1.0
Min, Max	-8, 9	-2, 2

Norfolk QoL-DN score = composite of 35 quality of life questions; lower scores indicate higher quality of life (range = -4 to 136). Nonmissing scores for items 27-33 imputed for patients who reported an impact due to COVID-19 pandemic. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 3.8
Norfolk Quality of Life - Diabetic Neuropathy (QoL-DN) Domain Scores: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Norfolk QoL-DN Domain: Autonomic

Genotype: V30M

Subgroup Visit	Vutrisiran (HELIOS-A) (N=54)	Patisiran (HELIOS-A) (N=20)
Baseline		
n	53	20
Mean (SD)	2.8 (2.9)	3.1 (2.7)
SE	0.4	0.6
Median	2.0	2.0
Min, Max	0, 11	0, 10
Month 9		
Actual Value		
n	52	20
Mean (SD)	1.9 (2.1)	2.0 (1.7)
SE	0.3	0.4
Median	1.0	2.5
Min, Max	0, 10	0, 6
Change from baseline		
n	51	20
Mean (SD)	-0.9 (2.2)	-1.1 (1.4)
SE	0.3	0.3
Median	0.0	-1.0
Min, Max	-7, 4	-4, 1

Norfolk QoL-DN score = composite of 35 quality of life questions; lower scores indicate higher quality of life (range = -4 to 136). Nonmissing scores for items 27-33 imputed for patients who reported an impact due to COVID-19 pandemic. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

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Table 3.8
Norfolk Quality of Life - Diabetic Neuropathy (QoL-DN) Domain Scores: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Norfolk QoL-DN Domain: Autonomic

Genotype: V30M

Subgroup Visit	Vutrisiran (HELIOS-A) (N=54)	Patisiran (HELIOS-A) (N=20)
Month 18		
Actual Value		
n	52	20
Mean (SD)	2.2 (2.2)	2.4 (2.2)
SE	0.3	0.5
Median	2.0	2.0
Min, Max	0, 9	0, 8
Change from baseline		
n	51	20
Mean (SD)	-0.6 (2.8)	-0.8 (1.5)
SE	0.4	0.3
Median	0.0	-1.0
Min, Max	-9, 9	-4, 2

Norfolk QoL-DN score = composite of 35 quality of life questions; lower scores indicate higher quality of life (range = -4 to 136). Nonmissing scores for items 27-33 imputed for patients who reported an impact due to COVID-19 pandemic. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

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Table 3.8
Norfolk Quality of Life - Diabetic Neuropathy (QoL-DN) Domain Scores: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Norfolk QoL-DN Domain: Autonomic

Genotype: non-V30M

Subgroup Visit	Vutrisiran (HELIOS-A) (N=68)	Patisiran (HELIOS-A) (N=22)
Baseline		
n	68	22
Mean (SD)	2.6 (2.9)	2.9 (2.9)
SE	0.3	0.6
Median	1.5	2.0
Min, Max	0, 12	0, 9
Month 9		
Actual Value		
n	64	20
Mean (SD)	2.4 (2.3)	3.3 (2.4)
SE	0.3	0.5
Median	2.0	3.5
Min, Max	0, 8	0, 9
Change from baseline		
n	64	20
Mean (SD)	-0.1 (2.2)	0.2 (1.5)
SE	0.3	0.3
Median	0.0	0.0
Min, Max	-6, 4	-2, 3

Norfolk QoL-DN score = composite of 35 quality of life questions; lower scores indicate higher quality of life (range = -4 to 136). Nonmissing scores for items 27-33 imputed for patients who reported an impact due to COVID-19 pandemic. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

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Table 3.8
Norfolk Quality of Life - Diabetic Neuropathy (QoL-DN) Domain Scores: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Norfolk QoL-DN Domain: Autonomic

Genotype: non-V30M

Subgroup Visit	Vutrisiran (HELIOS-A) (N=68)	Patisiran (HELIOS-A) (N=22)
Month 18		
Actual Value		
n	62	18
Mean (SD)	2.1 (1.8)	2.6 (2.6)
SE	0.2	0.6
Median	2.0	2.0
Min, Max	0, 6	0, 8
Change from baseline		
n	62	18
Mean (SD)	-0.5 (2.1)	-0.4 (1.3)
SE	0.3	0.3
Median	0.0	0.0
Min, Max	-8, 5	-2, 2

Norfolk QoL-DN score = composite of 35 quality of life questions; lower scores indicate higher quality of life (range = -4 to 136). Nonmissing scores for items 27-33 imputed for patients who reported an impact due to COVID-19 pandemic. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

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Table 3.8
Norfolk Quality of Life - Diabetic Neuropathy (QoL-DN) Domain Scores: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Norfolk QoL-DN Domain: Autonomic

FAP Stage: I

Subgroup Visit	Vutrisiran (HELIOS-A) (N=84)	Patisiran (HELIOS-A) (N=31)
Baseline		
n	83	31
Mean (SD)	2.7 (2.8)	3.1 (2.6)
SE	0.3	0.5
Median	2.0	2.0
Min, Max	0, 12	0, 10
Month 9		
Actual Value		
n	82	30
Mean (SD)	2.1 (2.2)	2.4 (2.1)
SE	0.2	0.4
Median	1.5	2.5
Min, Max	0, 10	0, 6
Change from baseline		
n	81	30
Mean (SD)	-0.5 (2.2)	-0.8 (1.1)
SE	0.2	0.2
Median	0.0	-1.0
Min, Max	-7, 4	-4, 1

Norfolk QoL-DN score = composite of 35 quality of life questions; lower scores indicate higher quality of life (range = -4 to 136). Nonmissing scores for items 27-33 imputed for patients who reported an impact due to COVID-19 pandemic. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

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Table 3.8
Norfolk Quality of Life - Diabetic Neuropathy (QoL-DN) Domain Scores: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Norfolk QoL-DN Domain: Autonomic

FAP Stage: I

Subgroup Visit	Vutrisiran (HELIOS-A) (N=84)	Patisiran (HELIOS-A) (N=31)
Month 18		
Actual Value		
n	81	30
Mean (SD)	2.2 (2.1)	2.6 (2.5)
SE	0.2	0.5
Median	2.0	2.0
Min, Max	0, 9	0, 8
Change from baseline		
n	80	30
Mean (SD)	-0.4 (2.5)	-0.7 (1.3)
SE	0.3	0.2
Median	0.0	-1.0
Min, Max	-9, 9	-3, 2

Norfolk QoL-DN score = composite of 35 quality of life questions; lower scores indicate higher quality of life (range = -4 to 136). Nonmissing scores for items 27-33 imputed for patients who reported an impact due to COVID-19 pandemic. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

Alnylam Pharmaceuticals Inc.
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Table 3.8
Norfolk Quality of Life - Diabetic Neuropathy (QoL-DN) Domain Scores: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Norfolk QoL-DN Domain: Autonomic

FAP Stage: II&III

Subgroup Visit	Vutrisiran (HELIOS-A) (N=38)	Patisiran (HELIOS-A) (N=11)
Baseline		
n	38	11
Mean (SD)	2.7 (3.0)	2.5 (3.2)
SE	0.5	1.0
Median	1.5	1.0
Min, Max	0, 11	0, 9
Month 9		
Actual Value		
n	34	10
Mean (SD)	2.3 (2.2)	3.4 (2.5)
SE	0.4	0.8
Median	2.0	3.0
Min, Max	0, 8	0, 9
Change from baseline		
n	34	10
Mean (SD)	-0.4 (2.3)	0.6 (2.1)
SE	0.4	0.7
Median	0.0	0.5
Min, Max	-6, 4	-4, 3

Norfolk QoL-DN score = composite of 35 quality of life questions; lower scores indicate higher quality of life (range = -4 to 136). Nonmissing scores for items 27-33 imputed for patients who reported an impact due to COVID-19 pandemic. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

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Table 3.8
Norfolk Quality of Life - Diabetic Neuropathy (QoL-DN) Domain Scores: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Norfolk QoL-DN Domain: Autonomic

FAP Stage: II&III

Subgroup Visit	Vutrisiran (HELIOS-A) (N=38)	Patisiran (HELIOS-A) (N=11)
Month 18		
Actual Value		
n	33	8
Mean (SD)	2.0 (1.7)	2.1 (1.6)
SE	0.3	0.6
Median	2.0	2.5
Min, Max	0, 6	0, 4
Change from baseline		
n	33	8
Mean (SD)	-0.8 (2.4)	-0.3 (1.8)
SE	0.4	0.6
Median	0.0	0.0
Min, Max	-8, 3	-4, 2

Norfolk QoL-DN score = composite of 35 quality of life questions; lower scores indicate higher quality of life (range = -4 to 136). Nonmissing scores for items 27-33 imputed for patients who reported an impact due to COVID-19 pandemic. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

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Table 3.8
Norfolk Quality of Life - Diabetic Neuropathy (QoL-DN) Domain Scores: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Norfolk QoL-DN Domain: Autonomic

Cardiac Subpopulation: Yes

Subgroup Visit	Vutrisiran (HELIOS-A) (N=40)	Patisiran (HELIOS-A) (N=14)
Baseline		
n	40	14
Mean (SD)	3.2 (3.1)	3.1 (3.2)
SE	0.5	0.9
Median	3.0	1.5
Min, Max	0, 12	0, 9
Month 9		
Actual Value		
n	38	14
Mean (SD)	2.5 (2.1)	3.1 (2.7)
SE	0.3	0.7
Median	2.5	3.0
Min, Max	0, 8	0, 9
Change from baseline		
n	38	14
Mean (SD)	-0.5 (2.3)	0.0 (1.8)
SE	0.4	0.5
Median	0.0	0.0
Min, Max	-6, 4	-4, 3

Norfolk QoL-DN score = composite of 35 quality of life questions; lower scores indicate higher quality of life (range = -4 to 136). Nonmissing scores for items 27-33 imputed for patients who reported an impact due to COVID-19 pandemic. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

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Table 3.8
Norfolk Quality of Life - Diabetic Neuropathy (QoL-DN) Domain Scores: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Norfolk QoL-DN Domain: Autonomic

Cardiac Subpopulation: Yes

Subgroup Visit	Vutrisiran (HELIOS-A) (N=40)	Patisiran (HELIOS-A) (N=14)
Month 18		
Actual Value		
n	37	13
Mean (SD)	2.5 (1.8)	2.3 (2.3)
SE	0.3	0.6
Median	2.0	2.0
Min, Max	0, 6	0, 8
Change from baseline		
n	37	13
Mean (SD)	-0.7 (2.3)	-0.3 (1.8)
SE	0.4	0.5
Median	0.0	0.0
Min, Max	-8, 5	-4, 2

Norfolk QoL-DN score = composite of 35 quality of life questions; lower scores indicate higher quality of life (range = -4 to 136). Nonmissing scores for items 27-33 imputed for patients who reported an impact due to COVID-19 pandemic. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 3.8
Norfolk Quality of Life - Diabetic Neuropathy (QoL-DN) Domain Scores: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Norfolk QoL-DN Domain: Autonomic

Cardiac Subpopulation: No

Subgroup Visit	Vutrisiran (HELIOS-A) (N=82)	Patisiran (HELIOS-A) (N=28)
Baseline		
n	81	28
Mean (SD)	2.4 (2.7)	2.9 (2.6)
SE	0.3	0.5
Median	2.0	2.0
Min, Max	0, 11	0, 10
Month 9		
Actual Value		
n	78	26
Mean (SD)	2.0 (2.3)	2.4 (1.9)
SE	0.3	0.4
Median	1.0	3.0
Min, Max	0, 10	0, 6
Change from baseline		
n	77	26
Mean (SD)	-0.4 (2.2)	-0.7 (1.4)
SE	0.2	0.3
Median	0.0	-1.0
Min, Max	-7, 4	-4, 3

Norfolk QoL-DN score = composite of 35 quality of life questions; lower scores indicate higher quality of life (range = -4 to 136). Nonmissing scores for items 27-33 imputed for patients who reported an impact due to COVID-19 pandemic. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

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Table 3.8
Norfolk Quality of Life - Diabetic Neuropathy (QoL-DN) Domain Scores: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Norfolk QoL-DN Domain: Autonomic

Cardiac Subpopulation: No

Subgroup Visit	Vutrisiran (HELIOS-A) (N=82)	Patisiran (HELIOS-A) (N=28)
Month 18		
Actual Value		
n	77	25
Mean (SD)	2.0 (2.1)	2.6 (2.4)
SE	0.2	0.5
Median	2.0	2.0
Min, Max	0, 9	0, 8
Change from baseline		
n	76	25
Mean (SD)	-0.5 (2.5)	-0.7 (1.2)
SE	0.3	0.2
Median	0.0	-1.0
Min, Max	-9, 9	-3, 2

Norfolk QoL-DN score = composite of 35 quality of life questions; lower scores indicate higher quality of life (range = -4 to 136). Nonmissing scores for items 27-33 imputed for patients who reported an impact due to COVID-19 pandemic. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 3.8
Norfolk Quality of Life - Diabetic Neuropathy (QoL-DN) Domain Scores: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Norfolk QoL-DN Domain: Autonomic

Weight (kg): <65

Subgroup Visit	Vutrisiran (HELIOS-A) (N=46)	Patisiran (HELIOS-A) (N=15)
Baseline		
n	46	15
Mean (SD)	3.5 (3.4)	4.7 (2.7)
SE	0.5	0.7
Median	3.0	5.0
Min, Max	0, 12	1, 10
Month 9		
Actual Value		
n	44	15
Mean (SD)	2.9 (2.6)	3.3 (1.9)
SE	0.4	0.5
Median	3.0	3.0
Min, Max	0, 10	0, 6
Change from baseline		
n	44	15
Mean (SD)	-0.5 (2.6)	-1.3 (1.4)
SE	0.4	0.4
Median	0.0	-1.0
Min, Max	-7, 4	-4, 1

Norfolk QoL-DN score = composite of 35 quality of life questions; lower scores indicate higher quality of life (range = -4 to 136). Nonmissing scores for items 27-33 imputed for patients who reported an impact due to COVID-19 pandemic. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

Data transfer: 20OCT2021, Extract Date: 18OCT2021, Data cutoff: 26AUG2021

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Table 3.8
Norfolk Quality of Life - Diabetic Neuropathy (QoL-DN) Domain Scores: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Norfolk QoL-DN Domain: Autonomic

Weight (kg): <65

Subgroup Visit	Vutrisiran (HELIOS-A) (N=46)	Patisiran (HELIOS-A) (N=15)
Month 18		
Actual Value		
n	42	15
Mean (SD)	2.7 (2.2)	3.9 (2.3)
SE	0.3	0.6
Median	2.5	4.0
Min, Max	0, 9	1, 8
Change from baseline		
n	42	15
Mean (SD)	-0.9 (2.6)	-0.7 (1.7)
SE	0.4	0.4
Median	0.0	-1.0
Min, Max	-9, 3	-4, 2

Norfolk QoL-DN score = composite of 35 quality of life questions; lower scores indicate higher quality of life (range = -4 to 136). Nonmissing scores for items 27-33 imputed for patients who reported an impact due to COVID-19 pandemic. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 3.8
Norfolk Quality of Life - Diabetic Neuropathy (QoL-DN) Domain Scores: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Norfolk QoL-DN Domain: Autonomic

Weight (kg): ≥65

Subgroup Visit	Vutrisiran (HELIOS-A) (N=76)	Patisiran (HELIOS-A) (N=27)
Baseline		
n	75	27
Mean (SD)	2.2 (2.4)	2.0 (2.4)
SE	0.3	0.5
Median	2.0	1.0
Min, Max	0, 8	0, 9
Month 9		
Actual Value		
n	72	25
Mean (SD)	1.7 (1.8)	2.2 (2.3)
SE	0.2	0.5
Median	1.0	2.0
Min, Max	0, 7	0, 9
Change from baseline		
n	71	25
Mean (SD)	-0.4 (2.0)	0.0 (1.4)
SE	0.2	0.3
Median	0.0	0.0
Min, Max	-6, 4	-2, 3

Norfolk QoL-DN score = composite of 35 quality of life questions; lower scores indicate higher quality of life (range = -4 to 136). Nonmissing scores for items 27-33 imputed for patients who reported an impact due to COVID-19 pandemic. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Table 3.8
Norfolk Quality of Life - Diabetic Neuropathy (QoL-DN) Domain Scores: Change from Baseline to Month 18, Descriptives by Visit and Subgroups
mITT Population

Norfolk QoL-DN Domain: Autonomic

Weight (kg): ≥65

Subgroup Visit	Vutrisiran (HELIOS-A) (N=76)	Patisiran (HELIOS-A) (N=27)
Month 18		
Actual Value		
n	72	23
Mean (SD)	1.8 (1.9)	1.5 (1.9)
SE	0.2	0.4
Median	2.0	1.0
Min, Max	0, 9	0, 8
Change from baseline		
n	71	23
Mean (SD)	-0.3 (2.3)	-0.5 (1.2)
SE	0.3	0.3
Median	0.0	0.0
Min, Max	-6, 9	-2, 2

Norfolk QoL-DN score = composite of 35 quality of life questions; lower scores indicate higher quality of life (range = -4 to 136). Nonmissing scores for items 27-33 imputed for patients who reported an impact due to COVID-19 pandemic. Assessments after initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE were included in analysis.

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Subgruppenanalysen zum Endpunkt „Unerwünschte Ereignisse, differenziert nach Schweregrad“

Gesamtrate UE jeglichen Schweregrades

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Table 11.15
Treatment-Emergent Adverse Events: Subgroup Analysis of Overall Summary During the 18-Month Treatment Period
Safety Population

At least 1 AE

Subgroup Statistics	Vutrisiran (HELIOS-A) (N=122) n (%)	Patisiran (HELIOS-A) (N=42) n (%)
Age (years)		
<65, n/N1 (%)	73/ 76 (96.1)	30/ 31 (96.8)
Risk difference (Vutrisiran - Patisiran), (95% CI)	-0.722 (-8.327, 6.884)	
Odds ratio (Vutrisiran/Patisiran), (95% CI)	0.811 (0.081, 8.112)	
Relative risk (Vutrisiran/Patisiran), (95% CI)	0.993 (0.917, 1.074)	
P-value [1]	0.8523	
≥65, n/N1 (%)	46/ 46 (100.0)	11/ 11 (100.0)
Risk difference (Vutrisiran - Patisiran), (95% CI)	0.000 (-)	
Odds ratio (Vutrisiran/Patisiran), (95% CI)	4.043 (0.076, 214.825)	
Relative risk (Vutrisiran/Patisiran), (95% CI)	1.032 (0.914, 1.166)	
P-value [1]	0.6077	
P-value of Treatment*Age [2]	0.5558	

TEAE = Treatment-emergent adverse event = AE with onset or worsening in severity after first dose through last dose + 84 days (vutrisiran) or + 28 days (patisiran), or AE considered treatment-related at any time after first dose.
Unstratified relative risk (RR), odds ratio (OR), and risk difference (RD) were presented. In estimation of the OR and RR, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the RD.
[1] p-value based on the Wald test testing whether the relative risk equals to 1.
[2] p-value from a logistic regression using the penalized likelihood estimation (the FIRTH option) and with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Table 11.15
Treatment-Emergent Adverse Events: Subgroup Analysis of Overall Summary During the 18-Month Treatment Period
Safety Population

At least 1 AE

Subgroup Statistics	Vutrisiran (HELIOS-A) (N=122) n (%)	Patisiran (HELIOS-A) (N=42) n (%)
Sex		
Male, n/N1 (%)	76/ 79 (96.2)	26/ 27 (96.3)
Risk difference (Vutrisiran - Patisiran), (95% CI)	-0.094 (-8.371, 8.183)	
Odds ratio (Vutrisiran/Patisiran), (95% CI)	0.974 (0.097, 9.782)	
Relative risk (Vutrisiran/Patisiran), (95% CI)	0.999 (0.917, 1.089)	
P-value [1]	0.9823	
Female, n/N1 (%)	43/ 43 (100.0)	15/ 15 (100.0)
Risk difference (Vutrisiran - Patisiran), (95% CI)	0.000 (-)	
Odds ratio (Vutrisiran/Patisiran), (95% CI)	2.806 (0.053, 147.598)	
Relative risk (Vutrisiran/Patisiran), (95% CI)	1.021 (0.929, 1.121)	
P-value [1]	0.6703	
P-value of Treatment*Sex [2]	0.7221	

TEAE = Treatment-emergent adverse event = AE with onset or worsening in severity after first dose through last dose + 84 days (vutrisiran) or + 28 days (patisiran), or AE considered treatment-related at any time after first dose.
Unstratified relative risk (RR), odds ratio (OR), and risk difference (RD) were presented. In estimation of the OR and RR, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the RD.
[1] p-value based on the Wald test testing whether the relative risk equals to 1.
[2] p-value from a logistic regression using the penalized likelihood estimation (the FIRTH option) and with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Alnylam Pharmaceuticals Inc.
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Table 11.15
Treatment-Emergent Adverse Events: Subgroup Analysis of Overall Summary During the 18-Month Treatment Period
Safety Population

At least 1 AE

Subgroup Statistics	Vutrisiran (HELIOS-A) (N=122) n (%)	Patisiran (HELIOS-A) (N=42) n (%)
Race		
White, n/N1 (%)	85/ 86 (98.8)	28/ 29 (96.6)
Risk difference (Vutrisiran - Patisiran), (95% CI)	2.285 (-4.731, 9.302)	
Odds ratio (Vutrisiran/Patisiran), (95% CI)	3.036 (0.184, 50.147)	
Relative risk (Vutrisiran/Patisiran), (95% CI)	1.024 (0.952, 1.101)	
P-value [1]	0.5271	
All Other Races, n/N1 (%)	34/ 36 (94.4)	13/ 13 (100.0)
Risk difference (Vutrisiran - Patisiran), (95% CI)	-5.556 (-13.038, 1.927)	
Odds ratio (Vutrisiran/Patisiran), (95% CI)	0.511 (0.023, 11.356)	
Relative risk (Vutrisiran/Patisiran), (95% CI)	0.967 (0.847, 1.105)	
P-value [1]	0.6206	
P-value of Treatment*Race [2]	0.3813	

TEAE = Treatment-emergent adverse event = AE with onset or worsening in severity after first dose through last dose + 84 days (vutrisiran) or + 28 days (patisiran), or AE considered treatment-related at any time after first dose.
Unstratified relative risk (RR), odds ratio (OR), and risk difference (RD) were presented. In estimation of the OR and RR, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the RD.
[1] p-value based on the Wald test testing whether the relative risk equals to 1.
[2] p-value from a logistic regression using the penalized likelihood estimation (the FIRTH option) and with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Table 11.15
Treatment-Emergent Adverse Events: Subgroup Analysis of Overall Summary During the 18-Month Treatment Period
Safety Population

At least 1 AE

Subgroup Statistics	Vutrisiran (HELIOS-A) (N=122) n (%)	Patisiran (HELIOS-A) (N=42) n (%)
Region		
North America, n/N1 (%)	27/ 27 (100.0)	8/ 8 (100.0)
Risk difference (Vutrisiran - Patisiran), (95% CI)	0.000 (-)	
Odds ratio (Vutrisiran/Patisiran), (95% CI)	3.235 (0.060, 175.704)	
Relative risk (Vutrisiran/Patisiran), (95% CI)	1.040 (0.881, 1.228)	
P-value [1]	0.6443	
Western Europe, n/N1 (%)	42/ 42 (100.0)	20/ 20 (100.0)
Risk difference (Vutrisiran - Patisiran), (95% CI)	0.000 (-)	
Odds ratio (Vutrisiran/Patisiran), (95% CI)	2.073 (0.040, 108.232)	
Relative risk (Vutrisiran/Patisiran), (95% CI)	1.012 (0.940, 1.091)	
P-value [1]	0.7434	
Rest of World, n/N1 (%)	50/ 53 (94.3)	13/ 14 (92.9)
Risk difference (Vutrisiran - Patisiran), (95% CI)	1.482 (-13.373, 16.338)	
Odds ratio (Vutrisiran/Patisiran), (95% CI)	1.282 (0.123, 13.362)	
Relative risk (Vutrisiran/Patisiran), (95% CI)	1.016 (0.866, 1.192)	
P-value [1]	0.8457	
P-value of Treatment*Region [2]	0.9557	

TEAE = Treatment-emergent adverse event = AE with onset or worsening in severity after first dose through last dose + 84 days (vutrisiran) or + 28 days (patisiran), or AE considered treatment-related at any time after first dose.
Unstratified relative risk (RR), odds ratio (OR), and risk difference (RD) were presented. In estimation of the OR and RR, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the RD.
[1] p-value based on the Wald test testing whether the relative risk equals to 1.
[2] p-value from a logistic regression using the penalized likelihood estimation (the FIRTH option) and with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Table 11.15
Treatment-Emergent Adverse Events: Subgroup Analysis of Overall Summary During the 18-Month Treatment Period
Safety Population

At least 1 AE

Subgroup Statistics	Vutrisiran (HELIOS-A) (N=122) n (%)	Patisiran (HELIOS-A) (N=42) n (%)
Baseline NIS		
<50, n/N1 (%)	77/ 78 (98.7)	27/ 27 (100.0)
Risk difference (Vutrisiran - Patisiran), (95% CI)	-1.282 (-3.779, 1.215)	
Odds ratio (Vutrisiran/Patisiran), (95% CI)	0.939 (0.037, 23.748)	
Relative risk (Vutrisiran/Patisiran), (95% CI)	0.999 (0.942, 1.059)	
P-value [1]	0.9693	
≥50, n/N1 (%)	42/ 44 (95.5)	14/ 15 (93.3)
Risk difference (Vutrisiran - Patisiran), (95% CI)	2.121 (-11.923, 16.165)	
Odds ratio (Vutrisiran/Patisiran), (95% CI)	1.500 (0.126, 17.831)	
Relative risk (Vutrisiran/Patisiran), (95% CI)	1.023 (0.880, 1.188)	
P-value [1]	0.7688	
P-value of Treatment*Baseline NIS [2]	0.7544	

TEAE = Treatment-emergent adverse event = AE with onset or worsening in severity after first dose through last dose + 84 days (vutrisiran) or + 28 days (patisiran), or AE considered treatment-related at any time after first dose.
Unstratified relative risk (RR), odds ratio (OR), and risk difference (RD) were presented. In estimation of the OR and RR, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the RD.
[1] p-value based on the Wald test testing whether the relative risk equals to 1.
[2] p-value from a logistic regression using the penalized likelihood estimation (the FIRTH option) and with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Table 11.15
Treatment-Emergent Adverse Events: Subgroup Analysis of Overall Summary During the 18-Month Treatment Period
Safety Population

At least 1 AE

Subgroup Statistics	Vutrisiran (HELIOS-A) (N=122) n (%)	Patisiran (HELIOS-A) (N=42) n (%)
Previous Tetramer Stabilizer Use		
Yes, n/N1 (%)	72/ 75 (96.0)	32/ 33 (97.0)
Risk difference (Vutrisiran - Patisiran), (95% CI)	-0.970 (-8.310, 6.370)	
Odds ratio (Vutrisiran/Patisiran), (95% CI)	0.750 (0.075, 7.489)	
Relative risk (Vutrisiran/Patisiran), (95% CI)	0.990 (0.918, 1.068)	
P-value [1]	0.7954	
No, n/N1 (%)	47/ 47 (100.0)	9/ 9 (100.0)
Risk difference (Vutrisiran - Patisiran), (95% CI)	0.000 (-)	
Odds ratio (Vutrisiran/Patisiran), (95% CI)	5.000 (0.093, 267.944)	
Relative risk (Vutrisiran/Patisiran), (95% CI)	1.042 (0.901, 1.204)	
P-value [1]	0.5814	
P-value of Treatment*Previous Tetramer Stabilizer Use [2]	0.4776	

TEAE = Treatment-emergent adverse event = AE with onset or worsening in severity after first dose through last dose + 84 days (vutrisiran) or + 28 days (patisiran), or AE considered treatment-related at any time after first dose.
Unstratified relative risk (RR), odds ratio (OR), and risk difference (RD) were presented. In estimation of the OR and RR, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the RD.
[1] p-value based on the Wald test testing whether the relative risk equals to 1.
[2] p-value from a logistic regression using the penalized likelihood estimation (the FIRTH option) and with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Table 11.15
Treatment-Emergent Adverse Events: Subgroup Analysis of Overall Summary During the 18-Month Treatment Period
Safety Population

At least 1 AE

Subgroup Statistics	Vutrisiran (HELIOS-A) (N=122) n (%)	Patisiran (HELIOS-A) (N=42) n (%)
Genotype		
V30M, n/N1 (%)	54/ 54 (100.0)	20/ 20 (100.0)
Risk difference (Vutrisiran - Patisiran), (95% CI)	0.000 (-)	
Odds ratio (Vutrisiran/Patisiran), (95% CI)	2.659 (0.051, 138.443)	
Relative risk (Vutrisiran/Patisiran), (95% CI)	1.015 (0.945, 1.090)	
P-value [1]	0.6814	
non-V30M, n/N1 (%)	65/ 68 (95.6)	21/ 22 (95.5)
Risk difference (Vutrisiran - Patisiran), (95% CI)	0.134 (-9.846, 10.113)	
Odds ratio (Vutrisiran/Patisiran), (95% CI)	1.032 (0.102, 10.457)	
Relative risk (Vutrisiran/Patisiran), (95% CI)	1.001 (0.902, 1.112)	
P-value [1]	0.9791	
P-value of Treatment*Genotype [2]	0.7565	

TEAE = Treatment-emergent adverse event = AE with onset or worsening in severity after first dose through last dose + 84 days (vutrisiran) or + 28 days (patisiran), or AE considered treatment-related at any time after first dose.
Unstratified relative risk (RR), odds ratio (OR), and risk difference (RD) were presented. In estimation of the OR and RR, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the RD.
[1] p-value based on the Wald test testing whether the relative risk equals to 1.
[2] p-value from a logistic regression using the penalized likelihood estimation (the FIRTH option) and with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Table 11.15
Treatment-Emergent Adverse Events: Subgroup Analysis of Overall Summary During the 18-Month Treatment Period
Safety Population

At least 1 AE

Subgroup Statistics	Vutrisiran (HELIOS-A) (N=122) n (%)	Patisiran (HELIOS-A) (N=42) n (%)
FAP Stage		
I, n/N1 (%)	83/ 84 (98.8)	31/ 31 (100.0)
Risk difference (Vutrisiran - Patisiran), (95% CI)	-1.190 (-3.510, 1.129)	
Odds ratio (Vutrisiran/Patisiran), (95% CI)	0.884 (0.035, 22.264)	
Relative risk (Vutrisiran/Patisiran), (95% CI)	0.998 (0.947, 1.051)	
P-value [1]	0.9384	
II&III, n/N1 (%)	36/ 38 (94.7)	10/ 11 (90.9)
Risk difference (Vutrisiran - Patisiran), (95% CI)	3.828 (-14.585, 22.240)	
Odds ratio (Vutrisiran/Patisiran), (95% CI)	1.800 (0.148, 21.942)	
Relative risk (Vutrisiran/Patisiran), (95% CI)	1.042 (0.852, 1.275)	
P-value [1]	0.6881	
P-value of Treatment*FAP Stage [2]	0.6697	

TEAE = Treatment-emergent adverse event = AE with onset or worsening in severity after first dose through last dose + 84 days (vutrisiran) or + 28 days (patisiran), or AE considered treatment-related at any time after first dose.
Unstratified relative risk (RR), odds ratio (OR), and risk difference (RD) were presented. In estimation of the OR and RR, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the RD.
[1] p-value based on the Wald test testing whether the relative risk equals to 1.
[2] p-value from a logistic regression using the penalized likelihood estimation (the FIRTH option) and with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Table 11.15
Treatment-Emergent Adverse Events: Subgroup Analysis of Overall Summary During the 18-Month Treatment Period
Safety Population

At least 1 AE

Subgroup Statistics	Vutrisiran (HELIOS-A) (N=122) n (%)	Patisiran (HELIOS-A) (N=42) n (%)
Cardiac Subpopulation		
Yes, n/N1 (%)	39/ 40 (97.5)	13/ 14 (92.9)
Risk difference (Vutrisiran - Patisiran), (95% CI)	4.643 (-9.689, 18.975)	
Odds ratio (Vutrisiran/Patisiran), (95% CI)	3.000 (0.175, 51.450)	
Relative risk (Vutrisiran/Patisiran), (95% CI)	1.050 (0.901, 1.224)	
P-value [1]	0.5334	
No, n/N1 (%)	80/ 82 (97.6)	28/ 28 (100.0)
Risk difference (Vutrisiran - Patisiran), (95% CI)	-2.439 (-5.778, 0.900)	
Odds ratio (Vutrisiran/Patisiran), (95% CI)	0.565 (0.026, 12.124)	
Relative risk (Vutrisiran/Patisiran), (95% CI)	0.987 (0.928, 1.049)	
P-value [1]	0.6733	
P-value of Treatment*Cardiac Subpopulation [2]	0.4125	

TEAE = Treatment-emergent adverse event = AE with onset or worsening in severity after first dose through last dose + 84 days (vutrisiran) or + 28 days (patisiran), or AE considered treatment-related at any time after first dose.
Unstratified relative risk (RR), odds ratio (OR), and risk difference (RD) were presented. In estimation of the OR and RR, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the RD.
[1] p-value based on the Wald test testing whether the relative risk equals to 1.
[2] p-value from a logistic regression using the penalized likelihood estimation (the FIRTH option) and with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Table 11.15
Treatment-Emergent Adverse Events: Subgroup Analysis of Overall Summary During the 18-Month Treatment Period
Safety Population

At least 1 AE

Subgroup Statistics	Vutrisiran (HELIOS-A) (N=122) n (%)	Patisiran (HELIOS-A) (N=42) n (%)
Weight (kg)		
<65 kg, n/N1 (%)	44/ 46 (95.7)	15/ 15 (100.0)
Risk difference (Vutrisiran - Patisiran), (95% CI)	-4.348 (-10.241, 1.545)	
Odds ratio (Vutrisiran/Patisiran), (95% CI)	0.574 (0.026, 12.630)	
Relative risk (Vutrisiran/Patisiran), (95% CI)	0.977 (0.875, 1.092)	
P-value [1]	0.6860	
>=65 kg, n/N1 (%)	75/ 76 (98.7)	26/ 27 (96.3)
Risk difference (Vutrisiran - Patisiran), (95% CI)	2.388 (-5.182, 9.958)	
Odds ratio (Vutrisiran/Patisiran), (95% CI)	2.885 (0.174, 47.792)	
Relative risk (Vutrisiran/Patisiran), (95% CI)	1.025 (0.948, 1.108)	
P-value [1]	0.5403	
P-value of Treatment*Weight [2]	0.4263	

TEAE = Treatment-emergent adverse event = AE with onset or worsening in severity after first dose through last dose + 84 days (vutrisiran) or + 28 days (patisiran), or AE considered treatment-related at any time after first dose.
Unstratified relative risk (RR), odds ratio (OR), and risk difference (RD) were presented. In estimation of the OR and RR, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the RD.
[1] p-value based on the Wald test testing whether the relative risk equals to 1.
[2] p-value from a logistic regression using the penalized likelihood estimation (the FIRTH option) and with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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UE jeglichen Schweregrades nach SOC/PT

UE – SOC Erkrankungen des Ohrs und des Labyrinths

Für diesen Endpunkt wurden für kein Subgruppenmerkmal zehn oder mehr Ereignisse in den jeweiligen Subgruppenausprägungen berichtet. Daher werden, den Vorgaben des G-BA entsprechend, keine Subgruppenanalysen für diesen Endpunkt dargestellt.

UE – SOC Erkrankungen des Immunsystems

Für diesen Endpunkt wurden für die Subgruppenmerkmale Geschlecht, Region, Genotyp und Gewicht weniger als zehn Ereignisse in den jeweiligen Subgruppenausprägungen berichtet. Daher werden, den Vorgaben des G-BA entsprechend, keine Subgruppenanalysen für diese Subgruppenmerkmale dargestellt.

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Table 11.18
Treatment-Emergent Adverse Events of Immune System Disorders (System Organ Class) during the 18-Month Treatment Period: Subgroup Analysis
Safety Population

Subgroup Statistics	Vutrisiran (HELIOS-A) (N=122) n (%)	Patisiran (HELIOS-A) (N=42) n (%)
Age (years)		
<65, n/N1 (%)	2/ 76 (2.6)	10/ 31 (32.3)
Risk difference (Vutrisiran - Patisiran), (95% CI)	-29.626 (-46.471, -12.782)	
Odds ratio (Vutrisiran/Patisiran), (95% CI)	0.057 (0.012, 0.279)	
Relative risk (Vutrisiran/Patisiran), (95% CI)	0.082 (0.019, 0.351)	
P-value [1]	0.0008	
≥65, n/N1 (%)	1/ 46 (2.2)	0/ 11 (0)
Risk difference (Vutrisiran - Patisiran), (95% CI)	2.174 (-2.040, 6.388)	
Odds ratio (Vutrisiran/Patisiran), (95% CI)	0.758 (0.029, 19.857)	
Relative risk (Vutrisiran/Patisiran), (95% CI)	0.766 (0.033, 17.647)	
P-value [1]	0.8677	
P-value of Treatment*Age [2]	0.2022	

TEAE = Treatment-emergent adverse event = AE with onset or worsening in severity after first dose through last dose + 84 days (vutrisiran) or + 28 days (patisiran), or AE considered treatment-related at any time after first dose.
Unstratified relative risk (RR), odds ratio (OR), and risk difference (RD) were presented. In estimation of the OR and RR, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the RD.
[1] p-value based on the Wald test testing whether the relative risk equals to 1.
[2] p-value from a logistic regression using the penalized likelihood estimation (the FIRTH option) and with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Table 11.18
Treatment-Emergent Adverse Events of Immune System Disorders (System Organ Class) during the 18-Month Treatment Period: Subgroup Analysis
Safety Population

Subgroup Statistics	Vutrisiran (HELIOS-A) (N=122) n (%)	Patisiran (HELIOS-A) (N=42) n (%)
Race		
White, n/N1 (%)	2/ 86 (2.3)	8/ 29 (27.6)
Risk difference (Vutrisiran - Patisiran), (95% CI)	-25.261 (-41.836, -8.685)	
Odds ratio (Vutrisiran/Patisiran), (95% CI)	0.063 (0.012, 0.316)	
Relative risk (Vutrisiran/Patisiran), (95% CI)	0.084 (0.019, 0.375)	
P-value [1]	0.0012	
All Other Races, n/N1 (%)	1/ 36 (2.8)	2/ 13 (15.4)
Risk difference (Vutrisiran - Patisiran), (95% CI)	-12.607 (-32.941, 7.728)	
Odds ratio (Vutrisiran/Patisiran), (95% CI)	0.157 (0.013, 1.903)	
Relative risk (Vutrisiran/Patisiran), (95% CI)	0.181 (0.018, 1.828)	
P-value [1]	0.1473	
P-value of Treatment*Race [2]	0.4799	

TEAE = Treatment-emergent adverse event = AE with onset or worsening in severity after first dose through last dose + 84 days (vutrisiran) or + 28 days (patisiran), or AE considered treatment-related at any time after first dose.
Unstratified relative risk (RR), odds ratio (OR), and risk difference (RD) were presented. In estimation of the OR and RR, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the RD.
[1] p-value based on the Wald test testing whether the relative risk equals to 1.
[2] p-value from a logistic regression using the penalized likelihood estimation (the FIRTH option) and with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Table 11.18
Treatment-Emergent Adverse Events of Immune System Disorders (System Organ Class) during the 18-Month Treatment Period: Subgroup Analysis
Safety Population

Subgroup Statistics	Vutrisiran (HELIOS-A) (N=122) n (%)	Patisiran (HELIOS-A) (N=42) n (%)
Baseline NIS		
<50, n/N1 (%)	1/ 78 (1.3)	10/ 27 (37.0)
Risk difference (Vutrisiran - Patisiran), (95% CI)	-35.755 (-54.140, -17.370)	
Odds ratio (Vutrisiran/Patisiran), (95% CI)	0.022 (0.003, 0.184)	
Relative risk (Vutrisiran/Patisiran), (95% CI)	0.035 (0.005, 0.258)	
P-value [1]	0.0010	
≥50, n/N1 (%)	2/ 44 (4.5)	0/ 15 (0)
Risk difference (Vutrisiran - Patisiran), (95% CI)	4.545 (-1.609, 10.700)	
Odds ratio (Vutrisiran/Patisiran), (95% CI)	1.824 (0.083, 40.138)	
Relative risk (Vutrisiran/Patisiran), (95% CI)	1.778 (0.090, 35.081)	
P-value [1]	0.7053	
P-value of Treatment*Baseline NIS [2]	0.0306	

TEAE = Treatment-emergent adverse event = AE with onset or worsening in severity after first dose through last dose + 84 days (vutrisiran) or + 28 days (patisiran), or AE considered treatment-related at any time after first dose.
Unstratified relative risk (RR), odds ratio (OR), and risk difference (RD) were presented. In estimation of the OR and RR, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the RD.
[1] p-value based on the Wald test testing whether the relative risk equals to 1.
[2] p-value from a logistic regression using the penalized likelihood estimation (the FIRTH option) and with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Table 11.18
Treatment-Emergent Adverse Events of Immune System Disorders (System Organ Class) during the 18-Month Treatment Period: Subgroup Analysis
Safety Population

Subgroup Statistics	Vutrisiran (HELIOS-A) (N=122) n (%)	Patisiran (HELIOS-A) (N=42) n (%)
Previous Tetramer Stabilizer Use		
Yes, n/N1 (%)	3/ 75 (4.0)	8/ 33 (24.2)
Risk difference (Vutrisiran - Patisiran), (95% CI)	-20.242 (-35.522, -4.963)	
Odds ratio (Vutrisiran/Patisiran), (95% CI)	0.130 (0.032, 0.529)	
Relative risk (Vutrisiran/Patisiran), (95% CI)	0.165 (0.047, 0.583)	
P-value [1]	0.0051	
No, n/N1 (%)	0/ 47 (0)	2/ 9 (22.2)
Risk difference (Vutrisiran - Patisiran), (95% CI)	-22.222 (-49.383, 4.939)	
Odds ratio (Vutrisiran/Patisiran), (95% CI)	0.032 (0.001, 0.724)	
Relative risk (Vutrisiran/Patisiran), (95% CI)	0.042 (0.002, 0.803)	
P-value [1]	0.0353	
P-value of Treatment*Previous Tetramer Stabilizer Use [2]	0.3887	

TEAE = Treatment-emergent adverse event = AE with onset or worsening in severity after first dose through last dose + 84 days (vutrisiran) or + 28 days (patisiran), or AE considered treatment-related at any time after first dose.
Unstratified relative risk (RR), odds ratio (OR), and risk difference (RD) were presented. In estimation of the OR and RR, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the RD.
[1] p-value based on the Wald test testing whether the relative risk equals to 1.
[2] p-value from a logistic regression using the penalized likelihood estimation (the FIRTH option) and with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Table 11.18
Treatment-Emergent Adverse Events of Immune System Disorders (System Organ Class) during the 18-Month Treatment Period: Subgroup Analysis
Safety Population

Subgroup Statistics	Vutrisiran (HELIOS-A) (N=122) n (%)	Patisiran (HELIOS-A) (N=42) n (%)
FAP Stage		
I, n/N1 (%)	1/ 84 (1.2)	10/ 31 (32.3)
Risk difference (Vutrisiran - Patisiran), (95% CI)	-31.068 (-47.686, -14.449)	
Odds ratio (Vutrisiran/Patisiran), (95% CI)	0.025 (0.003, 0.209)	
Relative risk (Vutrisiran/Patisiran), (95% CI)	0.037 (0.005, 0.277)	
P-value [1]	0.0013	
II&III, n/N1 (%)	2/ 38 (5.3)	0/ 11 (0)
Risk difference (Vutrisiran - Patisiran), (95% CI)	5.263 (-1.837, 12.363)	
Odds ratio (Vutrisiran/Patisiran), (95% CI)	1.575 (0.070, 35.245)	
Relative risk (Vutrisiran/Patisiran), (95% CI)	1.538 (0.079, 29.887)	
P-value [1]	0.7759	
P-value of Treatment*FAP Stage [2]	0.0461	

TEAE = Treatment-emergent adverse event = AE with onset or worsening in severity after first dose through last dose + 84 days (vutrisiran) or + 28 days (patisiran), or AE considered treatment-related at any time after first dose.
Unstratified relative risk (RR), odds ratio (OR), and risk difference (RD) were presented. In estimation of the OR and RR, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the RD.
[1] p-value based on the Wald test testing whether the relative risk equals to 1.
[2] p-value from a logistic regression using the penalized likelihood estimation (the FIRTH option) and with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Table 11.18
Treatment-Emergent Adverse Events of Immune System Disorders (System Organ Class) during the 18-Month Treatment Period: Subgroup Analysis
Safety Population

Subgroup Statistics	Vutrisiran (HELIOS-A) (N=122) n (%)	Patisiran (HELIOS-A) (N=42) n (%)
Cardiac Subpopulation		
Yes, n/N1 (%)	1/ 40 (2.5)	1/ 14 (7.1)
Risk difference (Vutrisiran - Patisiran), (95% CI)	-4.643 (-18.975, 9.689)	
Odds ratio (Vutrisiran/Patisiran), (95% CI)	0.333 (0.019, 5.717)	
Relative risk (Vutrisiran/Patisiran), (95% CI)	0.350 (0.023, 5.230)	
P-value [1]	0.4467	
No, n/N1 (%)	2/ 82 (2.4)	9/ 28 (32.1)
Risk difference (Vutrisiran - Patisiran), (95% CI)	-29.704 (-47.322, -12.086)	
Odds ratio (Vutrisiran/Patisiran), (95% CI)	0.053 (0.011, 0.265)	
Relative risk (Vutrisiran/Patisiran), (95% CI)	0.076 (0.017, 0.330)	
P-value [1]	0.0006	
P-value of Treatment*Cardiac Subpopulation [2]	0.2446	

TEAE = Treatment-emergent adverse event = AE with onset or worsening in severity after first dose through last dose + 84 days (vutrisiran) or + 28 days (patisiran), or AE considered treatment-related at any time after first dose.
Unstratified relative risk (RR), odds ratio (OR), and risk difference (RD) were presented. In estimation of the OR and RR, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the RD.
[1] p-value based on the Wald test testing whether the relative risk equals to 1.
[2] p-value from a logistic regression using the penalized likelihood estimation (the FIRTH option) and with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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UE – PT Reaktion im Zusammenhang mit einer Infusion

Für diesen Endpunkt wurden für die Subgruppenmerkmale Geschlecht, Abstammung, Region, Vorherige Behandlung mit Tetramer-Stabilisatoren, Genotyp, Kardiale Subpopulation und Gewicht weniger als zehn Ereignisse in den jeweiligen Subgruppenausprägungen berichtet. Daher werden, den Vorgaben des G-BA entsprechend, keine Subgruppenanalysen für diese Subgruppenmerkmale dargestellt.

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Table 11.19
Treatment-Emergent Adverse Events of Infusion-related Reactions (Preferred Term) during the 18-Month Treatment Period: Subgroup Analysis
Safety Population

Subgroup Statistics	Vutrisiran (HELIOS-A) (N=122) n (%)	Patisiran (HELIOS-A) (N=42) n (%)
Age (years)		
<65, n/N1 (%)	0/ 76 (0)	10/ 31 (32.3)
Risk difference (Vutrisiran - Patisiran), (95% CI)	-32.258 (-48.714, -15.802)	
Odds ratio (Vutrisiran/Patisiran), (95% CI)	0.013 (0.001, 0.238)	
Relative risk (Vutrisiran/Patisiran), (95% CI)	0.020 (0.001, 0.328)	
P-value [1]	0.0062	
≥65, n/N1 (%)	0/ 46 (0)	0/ 11 (0)
Risk difference (Vutrisiran - Patisiran), (95% CI)	-	
Odds ratio (Vutrisiran/Patisiran), (95% CI)	0.247 (0.005, 13.139)	
Relative risk (Vutrisiran/Patisiran), (95% CI)	0.255 (0.005, 12.220)	
P-value [1]	0.4891	
P-value of Treatment*Age [2]	0.2536	

TEAE = Treatment-emergent adverse event = AE with onset or worsening in severity after first dose through last dose + 84 days (vutrisiran) or + 28 days (patisiran), or AE considered treatment-related at any time after first dose.
Unstratified relative risk (RR), odds ratio (OR), and risk difference (RD) were presented. In estimation of the OR and RR, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the RD.
[1] p-value based on the Wald test testing whether the relative risk equals to 1.
[2] p-value from a logistic regression using the penalized likelihood estimation (the FIRTH option) and with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Table 11.19
Treatment-Emergent Adverse Events of Infusion-related Reactions (Preferred Term) during the 18-Month Treatment Period: Subgroup Analysis
Safety Population

Subgroup Statistics	Vutrisiran (HELIOS-A) (N=122) n (%)	Patisiran (HELIOS-A) (N=42) n (%)
Baseline NIS		
<50, n/N1 (%)	0/ 78 (0)	10/ 27 (37.0)
Risk difference (Vutrisiran - Patisiran), (95% CI)	-37.037 (-55.252, -18.822)	
Odds ratio (Vutrisiran/Patisiran), (95% CI)	0.011 (0.001, 0.190)	
Relative risk (Vutrisiran/Patisiran), (95% CI)	0.017 (0.001, 0.279)	
P-value [1]	0.0043	
≥50, n/N1 (%)	0/ 44 (0)	0/ 15 (0)
Risk difference (Vutrisiran - Patisiran), (95% CI)	-	
Odds ratio (Vutrisiran/Patisiran), (95% CI)	0.348 (0.007, 18.314)	
Relative risk (Vutrisiran/Patisiran), (95% CI)	0.356 (0.007, 17.186)	
P-value [1]	0.6013	
P-value of Treatment*Baseline NIS [2]	0.1699	

TEAE = Treatment-emergent adverse event = AE with onset or worsening in severity after first dose through last dose + 84 days (vutrisiran) or + 28 days (patisiran), or AE considered treatment-related at any time after first dose.
Unstratified relative risk (RR), odds ratio (OR), and risk difference (RD) were presented. In estimation of the OR and RR, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the RD.
[1] p-value based on the Wald test testing whether the relative risk equals to 1.
[2] p-value from a logistic regression using the penalized likelihood estimation (the FIRTH option) and with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Table 11.19
Treatment-Emergent Adverse Events of Infusion-related Reactions (Preferred Term) during the 18-Month Treatment Period: Subgroup Analysis
Safety Population

Subgroup Statistics	Vutrisiran (HELIOS-A) (N=122) n (%)	Patisiran (HELIOS-A) (N=42) n (%)
FAP Stage		
I, n/N1 (%)	0/ 84 (0)	10/ 31 (32.3)
Risk difference (Vutrisiran - Patisiran), (95% CI)	-32.258 (-48.714, -15.802)	
Odds ratio (Vutrisiran/Patisiran), (95% CI)	0.012 (0.001, 0.215)	
Relative risk (Vutrisiran/Patisiran), (95% CI)	0.018 (0.001, 0.297)	
P-value [1]	0.0050	
II&III, n/N1 (%)	0/ 38 (0)	0/ 11 (0)
Risk difference (Vutrisiran - Patisiran), (95% CI)	-	
Odds ratio (Vutrisiran/Patisiran), (95% CI)	0.299 (0.006, 15.904)	
Relative risk (Vutrisiran/Patisiran), (95% CI)	0.308 (0.006, 14.695)	
P-value [1]	0.5502	
P-value of Treatment*FAP Stage [2]	0.2101	

TEAE = Treatment-emergent adverse event = AE with onset or worsening in severity after first dose through last dose + 84 days (vutrisiran) or + 28 days (patisiran), or AE considered treatment-related at any time after first dose.
Unstratified relative risk (RR), odds ratio (OR), and risk difference (RD) were presented. In estimation of the OR and RR, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the RD.
[1] p-value based on the Wald test testing whether the relative risk equals to 1.
[2] p-value from a logistic regression using the penalized likelihood estimation (the FIRTH option) and with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Gesamtrate nicht-schwere UE

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Table 11.15
Treatment-Emergent Adverse Events: Subgroup Analysis of Overall Summary During the 18-Month Treatment Period
Safety Population

At least 1 non-severe AE

Subgroup Statistics	Vutrisiran (HELIOS-A) (N=122) n (%)	Patisiran (HELIOS-A) (N=42) n (%)
Age (years)		
<65, n/N1 (%)	73/ 76 (96.1)	30/ 31 (96.8)
Risk difference (Vutrisiran - Patisiran), (95% CI)	-0.722 (-8.327, 6.884)	
Odds ratio (Vutrisiran/Patisiran), (95% CI)	0.811 (0.081, 8.112)	
Relative risk (Vutrisiran/Patisiran), (95% CI)	0.993 (0.917, 1.074)	
P-value [1]	0.8523	
≥65, n/N1 (%)	45/ 46 (97.8)	10/ 11 (90.9)
Risk difference (Vutrisiran - Patisiran), (95% CI)	6.917 (-10.587, 24.421)	
Odds ratio (Vutrisiran/Patisiran), (95% CI)	4.500 (0.259, 78.204)	
Relative risk (Vutrisiran/Patisiran), (95% CI)	1.076 (0.888, 1.304)	
P-value [1]	0.4536	
P-value of Treatment*Age [2]	0.3701	

TEAE = Treatment-emergent adverse event = AE with onset or worsening in severity after first dose through last dose + 84 days (vutrisiran) or + 28 days (patisiran), or AE considered treatment-related at any time after first dose.
Unstratified relative risk (RR), odds ratio (OR), and risk difference (RD) were presented. In estimation of the OR and RR, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the RD.
[1] p-value based on the Wald test testing whether the relative risk equals to 1.
[2] p-value from a logistic regression using the penalized likelihood estimation (the FIRTH option) and with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Table 11.15
Treatment-Emergent Adverse Events: Subgroup Analysis of Overall Summary During the 18-Month Treatment Period
Safety Population

At least 1 non-severe AE

Subgroup Statistics	Vutrisiran (HELIOS-A) (N=122) n (%)	Patisiran (HELIOS-A) (N=42) n (%)
Sex		
Male, n/N1 (%)	75/ 79 (94.9)	25/ 27 (92.6)
Risk difference (Vutrisiran - Patisiran), (95% CI)	2.344 (-8.654, 13.342)	
Odds ratio (Vutrisiran/Patisiran), (95% CI)	1.500 (0.259, 8.690)	
Relative risk (Vutrisiran/Patisiran), (95% CI)	1.025 (0.911, 1.154)	
P-value [1]	0.6785	
Female, n/N1 (%)	43/ 43 (100.0)	15/ 15 (100.0)
Risk difference (Vutrisiran - Patisiran), (95% CI)	0.000 (-)	
Odds ratio (Vutrisiran/Patisiran), (95% CI)	2.806 (0.053, 147.598)	
Relative risk (Vutrisiran/Patisiran), (95% CI)	1.021 (0.929, 1.121)	
P-value [1]	0.6703	
P-value of Treatment*Sex [2]	0.8105	

TEAE = Treatment-emergent adverse event = AE with onset or worsening in severity after first dose through last dose + 84 days (vutrisiran) or + 28 days (patisiran), or AE considered treatment-related at any time after first dose.
Unstratified relative risk (RR), odds ratio (OR), and risk difference (RD) were presented. In estimation of the OR and RR, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the RD.
[1] p-value based on the Wald test testing whether the relative risk equals to 1.
[2] p-value from a logistic regression using the penalized likelihood estimation (the FIRTH option) and with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Table 11.15
Treatment-Emergent Adverse Events: Subgroup Analysis of Overall Summary During the 18-Month Treatment Period
Safety Population

At least 1 non-severe AE

Subgroup Statistics	Vutrisiran (HELIOS-A) (N=122) n (%)	Patisiran (HELIOS-A) (N=42) n (%)
Race		
White, n/N1 (%)	84/ 86 (97.7)	27/ 29 (93.1)
Risk difference (Vutrisiran - Patisiran), (95% CI)	4.571 (-5.186, 14.328)	
Odds ratio (Vutrisiran/Patisiran), (95% CI)	3.111 (0.418, 23.158)	
Relative risk (Vutrisiran/Patisiran), (95% CI)	1.049 (0.945, 1.164)	
P-value [1]	0.3677	
All Other Races, n/N1 (%)	34/ 36 (94.4)	13/ 13 (100.0)
Risk difference (Vutrisiran - Patisiran), (95% CI)	-5.556 (-13.038, 1.927)	
Odds ratio (Vutrisiran/Patisiran), (95% CI)	0.511 (0.023, 11.356)	
Relative risk (Vutrisiran/Patisiran), (95% CI)	0.967 (0.847, 1.105)	
P-value [1]	0.6206	
P-value of Treatment*Race [2]	0.3406	

TEAE = Treatment-emergent adverse event = AE with onset or worsening in severity after first dose through last dose + 84 days (vutrisiran) or + 28 days (patisiran), or AE considered treatment-related at any time after first dose.
Unstratified relative risk (RR), odds ratio (OR), and risk difference (RD) were presented. In estimation of the OR and RR, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the RD.
[1] p-value based on the Wald test testing whether the relative risk equals to 1.
[2] p-value from a logistic regression using the penalized likelihood estimation (the FIRTH option) and with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Table 11.15
Treatment-Emergent Adverse Events: Subgroup Analysis of Overall Summary During the 18-Month Treatment Period
Safety Population

At least 1 non-severe AE

Subgroup Statistics	Vutrisiran (HELIOS-A) (N=122) n (%)	Patisiran (HELIOS-A) (N=42) n (%)
Region		
North America, n/N1 (%)	27/ 27 (100.0)	8/ 8 (100.0)
Risk difference (Vutrisiran - Patisiran), (95% CI)	0.000 (-)	
Odds ratio (Vutrisiran/Patisiran), (95% CI)	3.235 (0.060, 175.704)	
Relative risk (Vutrisiran/Patisiran), (95% CI)	1.040 (0.881, 1.228)	
P-value [1]	0.6443	
Western Europe, n/N1 (%)	41/ 42 (97.6)	19/ 20 (95.0)
Risk difference (Vutrisiran - Patisiran), (95% CI)	2.619 (-7.987, 13.225)	
Odds ratio (Vutrisiran/Patisiran), (95% CI)	2.158 (0.128, 36.372)	
Relative risk (Vutrisiran/Patisiran), (95% CI)	1.028 (0.920, 1.148)	
P-value [1]	0.6313	
Rest of World, n/N1 (%)	50/ 53 (94.3)	13/ 14 (92.9)
Risk difference (Vutrisiran - Patisiran), (95% CI)	1.482 (-13.373, 16.338)	
Odds ratio (Vutrisiran/Patisiran), (95% CI)	1.282 (0.123, 13.362)	
Relative risk (Vutrisiran/Patisiran), (95% CI)	1.016 (0.866, 1.192)	
P-value [1]	0.8457	
P-value of Treatment*Region [2]	0.9527	

TEAE = Treatment-emergent adverse event = AE with onset or worsening in severity after first dose through last dose + 84 days (vutrisiran) or + 28 days (patisiran), or AE considered treatment-related at any time after first dose.
Unstratified relative risk (RR), odds ratio (OR), and risk difference (RD) were presented. In estimation of the OR and RR, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the RD.
[1] p-value based on the Wald test testing whether the relative risk equals to 1.
[2] p-value from a logistic regression using the penalized likelihood estimation (the FIRTH option) and with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Table 11.15
Treatment-Emergent Adverse Events: Subgroup Analysis of Overall Summary During the 18-Month Treatment Period
Safety Population

At least 1 non-severe AE

Subgroup Statistics	Vutrisiran (HELIOS-A) (N=122) n (%)	Patisiran (HELIOS-A) (N=42) n (%)
Baseline NIS		
<50, n/N1 (%)	77/ 78 (98.7)	27/ 27 (100.0)
Risk difference (Vutrisiran - Patisiran), (95% CI)	-1.282 (-3.779, 1.215)	
Odds ratio (Vutrisiran/Patisiran), (95% CI)	0.939 (0.037, 23.748)	
Relative risk (Vutrisiran/Patisiran), (95% CI)	0.999 (0.942, 1.059)	
P-value [1]	0.9693	
≥50, n/N1 (%)	41/ 44 (93.2)	13/ 15 (86.7)
Risk difference (Vutrisiran - Patisiran), (95% CI)	6.515 (-12.231, 25.261)	
Odds ratio (Vutrisiran/Patisiran), (95% CI)	2.103 (0.316, 13.985)	
Relative risk (Vutrisiran/Patisiran), (95% CI)	1.075 (0.868, 1.332)	
P-value [1]	0.5067	
P-value of Treatment*Baseline NIS [2]	0.6555	

TEAE = Treatment-emergent adverse event = AE with onset or worsening in severity after first dose through last dose + 84 days (vutrisiran) or + 28 days (patisiran), or AE considered treatment-related at any time after first dose.
Unstratified relative risk (RR), odds ratio (OR), and risk difference (RD) were presented. In estimation of the OR and RR, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the RD.
[1] p-value based on the Wald test testing whether the relative risk equals to 1.
[2] p-value from a logistic regression using the penalized likelihood estimation (the FIRTH option) and with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Table 11.15
Treatment-Emergent Adverse Events: Subgroup Analysis of Overall Summary During the 18-Month Treatment Period
Safety Population

At least 1 non-severe AE

Subgroup Statistics	Vutrisiran (HELIOS-A) (N=122) n (%)	Patisiran (HELIOS-A) (N=42) n (%)
Previous Tetramer Stabilizer Use		
Yes, n/N1 (%)	72/ 75 (96.0)	32/ 33 (97.0)
Risk difference (Vutrisiran - Patisiran), (95% CI)	-0.970 (-8.310, 6.370)	
Odds ratio (Vutrisiran/Patisiran), (95% CI)	0.750 (0.075, 7.489)	
Relative risk (Vutrisiran/Patisiran), (95% CI)	0.990 (0.918, 1.068)	
P-value [1]	0.7954	
No, n/N1 (%)	46/ 47 (97.9)	8/ 9 (88.9)
Risk difference (Vutrisiran - Patisiran), (95% CI)	8.983 (-11.959, 29.926)	
Odds ratio (Vutrisiran/Patisiran), (95% CI)	5.750 (0.325, 101.585)	
Relative risk (Vutrisiran/Patisiran), (95% CI)	1.101 (0.871, 1.392)	
P-value [1]	0.4216	
P-value of Treatment*Previous Tetramer Stabilizer Use [2]	0.2790	

TEAE = Treatment-emergent adverse event = AE with onset or worsening in severity after first dose through last dose + 84 days (vutrisiran) or + 28 days (patisiran), or AE considered treatment-related at any time after first dose.
Unstratified relative risk (RR), odds ratio (OR), and risk difference (RD) were presented. In estimation of the OR and RR, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the RD.
[1] p-value based on the Wald test testing whether the relative risk equals to 1.
[2] p-value from a logistic regression using the penalized likelihood estimation (the FIRTH option) and with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Table 11.15
Treatment-Emergent Adverse Events: Subgroup Analysis of Overall Summary During the 18-Month Treatment Period
Safety Population

At least 1 non-severe AE

Subgroup Statistics	Vutrisiran (HELIOS-A) (N=122) n (%)	Patisiran (HELIOS-A) (N=42) n (%)
Genotype		
V30M, n/N1 (%)	54/ 54 (100.0)	20/ 20 (100.0)
Risk difference (Vutrisiran - Patisiran), (95% CI)	0.000 (-)	
Odds ratio (Vutrisiran/Patisiran), (95% CI)	2.659 (0.051, 138.443)	
Relative risk (Vutrisiran/Patisiran), (95% CI)	1.015 (0.945, 1.090)	
P-value [1]	0.6814	
non-V30M, n/N1 (%)	64/ 68 (94.1)	20/ 22 (90.9)
Risk difference (Vutrisiran - Patisiran), (95% CI)	3.209 (-10.042, 16.459)	
Odds ratio (Vutrisiran/Patisiran), (95% CI)	1.600 (0.273, 9.394)	
Relative risk (Vutrisiran/Patisiran), (95% CI)	1.035 (0.896, 1.197)	
P-value [1]	0.6389	
P-value of Treatment*Genotype [2]	0.8500	

TEAE = Treatment-emergent adverse event = AE with onset or worsening in severity after first dose through last dose + 84 days (vutrisiran) or + 28 days (patisiran), or AE considered treatment-related at any time after first dose.
Unstratified relative risk (RR), odds ratio (OR), and risk difference (RD) were presented. In estimation of the OR and RR, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the RD.
[1] p-value based on the Wald test testing whether the relative risk equals to 1.
[2] p-value from a logistic regression using the penalized likelihood estimation (the FIRTH option) and with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Table 11.15
Treatment-Emergent Adverse Events: Subgroup Analysis of Overall Summary During the 18-Month Treatment Period
Safety Population

At least 1 non-severe AE

Subgroup Statistics	Vutrisiran (HELIOS-A) (N=122) n (%)	Patisiran (HELIOS-A) (N=42) n (%)
FAP Stage		
I, n/N1 (%)	83/ 84 (98.8)	30/ 31 (96.8)
Risk difference (Vutrisiran - Patisiran), (95% CI)	2.035 (-4.603, 8.673)	
Odds ratio (Vutrisiran/Patisiran), (95% CI)	2.767 (0.168, 45.637)	
Relative risk (Vutrisiran/Patisiran), (95% CI)	1.021 (0.954, 1.093)	
P-value [1]	0.5510	
II&III, n/N1 (%)	35/ 38 (92.1)	10/ 11 (90.9)
Risk difference (Vutrisiran - Patisiran), (95% CI)	1.196 (-17.833, 20.226)	
Odds ratio (Vutrisiran/Patisiran), (95% CI)	1.167 (0.109, 12.478)	
Relative risk (Vutrisiran/Patisiran), (95% CI)	1.013 (0.822, 1.248)	
P-value [1]	0.9023	
P-value of Treatment*FAP Stage [2]	0.6910	

TEAE = Treatment-emergent adverse event = AE with onset or worsening in severity after first dose through last dose + 84 days (vutrisiran) or + 28 days (patisiran), or AE considered treatment-related at any time after first dose.
Unstratified relative risk (RR), odds ratio (OR), and risk difference (RD) were presented. In estimation of the OR and RR, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the RD.
[1] p-value based on the Wald test testing whether the relative risk equals to 1.
[2] p-value from a logistic regression using the penalized likelihood estimation (the FIRTH option) and with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Table 11.15
Treatment-Emergent Adverse Events: Subgroup Analysis of Overall Summary During the 18-Month Treatment Period
Safety Population

At least 1 non-severe AE

Subgroup Statistics	Vutrisiran (HELIOS-A) (N=122) n (%)	Patisiran (HELIOS-A) (N=42) n (%)
Cardiac Subpopulation		
Yes, n/N1 (%)	38/ 40 (95.0)	13/ 14 (92.9)
Risk difference (Vutrisiran - Patisiran), (95% CI)	2.143 (-12.944, 17.230)	
Odds ratio (Vutrisiran/Patisiran), (95% CI)	1.462 (0.122, 17.482)	
Relative risk (Vutrisiran/Patisiran), (95% CI)	1.023 (0.870, 1.203)	
P-value [1]	0.7822	
No, n/N1 (%)	80/ 82 (97.6)	27/ 28 (96.4)
Risk difference (Vutrisiran - Patisiran), (95% CI)	1.132 (-6.509, 8.774)	
Odds ratio (Vutrisiran/Patisiran), (95% CI)	1.481 (0.129, 16.993)	
Relative risk (Vutrisiran/Patisiran), (95% CI)	1.012 (0.935, 1.095)	
P-value [1]	0.7723	
P-value of Treatment*Cardiac Subpopulation [2]	0.9866	

TEAE = Treatment-emergent adverse event = AE with onset or worsening in severity after first dose through last dose + 84 days (vutrisiran) or + 28 days (patisiran), or AE considered treatment-related at any time after first dose.
Unstratified relative risk (RR), odds ratio (OR), and risk difference (RD) were presented. In estimation of the OR and RR, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the RD.
[1] p-value based on the Wald test testing whether the relative risk equals to 1.
[2] p-value from a logistic regression using the penalized likelihood estimation (the FIRTH option) and with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Table 11.15
Treatment-Emergent Adverse Events: Subgroup Analysis of Overall Summary During the 18-Month Treatment Period
Safety Population

At least 1 non-severe AE

Subgroup Statistics	Vutrisiran (HELIOS-A) (N=122) n (%)	Patisiran (HELIOS-A) (N=42) n (%)
Weight (kg)		
<65 kg, n/N1 (%)	43/ 46 (93.5)	15/ 15 (100.0)
Risk difference (Vutrisiran - Patisiran), (95% CI)	-6.522 (-13.657, 0.613)	
Odds ratio (Vutrisiran/Patisiran), (95% CI)	0.401 (0.020, 8.210)	
Relative risk (Vutrisiran/Patisiran), (95% CI)	0.955 (0.848, 1.077)	
P-value [1]	0.4548	
>=65 kg, n/N1 (%)	75/ 76 (98.7)	25/ 27 (92.6)
Risk difference (Vutrisiran - Patisiran), (95% CI)	6.092 (-4.114, 16.297)	
Odds ratio (Vutrisiran/Patisiran), (95% CI)	6.000 (0.522, 69.028)	
Relative risk (Vutrisiran/Patisiran), (95% CI)	1.066 (0.955, 1.189)	
P-value [1]	0.2554	
P-value of Treatment*Weight [2]	0.1896	

TEAE = Treatment-emergent adverse event = AE with onset or worsening in severity after first dose through last dose + 84 days (vutrisiran) or + 28 days (patisiran), or AE considered treatment-related at any time after first dose.
Unstratified relative risk (RR), odds ratio (OR), and risk difference (RD) were presented. In estimation of the OR and RR, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the RD.
[1] p-value based on the Wald test testing whether the relative risk equals to 1.
[2] p-value from a logistic regression using the penalized likelihood estimation (the FIRTH option) and with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Table 11.15
Treatment-Emergent Adverse Events: Subgroup Analysis of Overall Summary During the 18-Month Treatment Period
Safety Population

At least 1 severe AE

Subgroup Statistics	Vutrisiran (HELIOS-A) (N=122) n (%)	Patisiran (HELIOS-A) (N=42) n (%)
Age (years)		
<65, n/N1 (%)	7/ 76 (9.2)	10/ 31 (32.3)
Risk difference (Vutrisiran - Patisiran), (95% CI)	-23.048 (-40.741, -5.354)	
Odds ratio (Vutrisiran/Patisiran), (95% CI)	0.213 (0.072, 0.629)	
Relative risk (Vutrisiran/Patisiran), (95% CI)	0.286 (0.120, 0.682)	
P-value [1]	0.0048	
≥65, n/N1 (%)	12/ 46 (26.1)	6/ 11 (54.5)
Risk difference (Vutrisiran - Patisiran), (95% CI)	-28.458 (-60.503, 3.586)	
Odds ratio (Vutrisiran/Patisiran), (95% CI)	0.294 (0.076, 1.143)	
Relative risk (Vutrisiran/Patisiran), (95% CI)	0.478 (0.231, 0.989)	
P-value [1]	0.0466	
P-value of Treatment*Age [2]	0.7097	

TEAE = Treatment-emergent adverse event = AE with onset or worsening in severity after first dose through last dose + 84 days (vutrisiran) or + 28 days (patisiran), or AE considered treatment-related at any time after first dose.
Unstratified relative risk (RR), odds ratio (OR), and risk difference (RD) were presented. In estimation of the OR and RR, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the RD.
[1] p-value based on the Wald test testing whether the relative risk equals to 1.
[2] p-value from a logistic regression using the penalized likelihood estimation (the FIRTH option) and with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Table 11.15
Treatment-Emergent Adverse Events: Subgroup Analysis of Overall Summary During the 18-Month Treatment Period
Safety Population

At least 1 severe AE

Subgroup Statistics	Vutrisiran (HELIOS-A) (N=122) n (%)	Patisiran (HELIOS-A) (N=42) n (%)
Sex		
Male, n/N1 (%)	14/ 79 (17.7)	9/ 27 (33.3)
Risk difference (Vutrisiran - Patisiran), (95% CI)	-15.612 (-35.286, 4.062)	
Odds ratio (Vutrisiran/Patisiran), (95% CI)	0.431 (0.161, 1.156)	
Relative risk (Vutrisiran/Patisiran), (95% CI)	0.532 (0.260, 1.086)	
P-value [1]	0.0830	
Female, n/N1 (%)	5/ 43 (11.6)	7/ 15 (46.7)
Risk difference (Vutrisiran - Patisiran), (95% CI)	-35.039 (-62.042, -8.035)	
Odds ratio (Vutrisiran/Patisiran), (95% CI)	0.150 (0.038, 0.596)	
Relative risk (Vutrisiran/Patisiran), (95% CI)	0.249 (0.093, 0.668)	
P-value [1]	0.0057	
P-value of Treatment*Sex [2]	0.2521	

TEAE = Treatment-emergent adverse event = AE with onset or worsening in severity after first dose through last dose + 84 days (vutrisiran) or + 28 days (patisiran), or AE considered treatment-related at any time after first dose.
Unstratified relative risk (RR), odds ratio (OR), and risk difference (RD) were presented. In estimation of the OR and RR, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the RD.
[1] p-value based on the Wald test testing whether the relative risk equals to 1.
[2] p-value from a logistic regression using the penalized likelihood estimation (the FIRTH option) and with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Table 11.15
Treatment-Emergent Adverse Events: Subgroup Analysis of Overall Summary During the 18-Month Treatment Period
Safety Population

At least 1 severe AE

Subgroup Statistics	Vutrisiran (HELIOS-A) (N=122) n (%)	Patisiran (HELIOS-A) (N=42) n (%)
Race		
White, n/N1 (%)	14/ 86 (16.3)	13/ 29 (44.8)
Risk difference (Vutrisiran - Patisiran), (95% CI)	-28.549 (-48.259, -8.838)	
Odds ratio (Vutrisiran/Patisiran), (95% CI)	0.239 (0.095, 0.606)	
Relative risk (Vutrisiran/Patisiran), (95% CI)	0.363 (0.194, 0.680)	
P-value [1]	0.0015	
All Other Races, n/N1 (%)	5/ 36 (13.9)	3/ 13 (23.1)
Risk difference (Vutrisiran - Patisiran), (95% CI)	-9.188 (-34.726, 16.350)	
Odds ratio (Vutrisiran/Patisiran), (95% CI)	0.538 (0.109, 2.660)	
Relative risk (Vutrisiran/Patisiran), (95% CI)	0.602 (0.167, 2.172)	
P-value [1]	0.4380	
P-value of Treatment*Race [2]	0.4092	

TEAE = Treatment-emergent adverse event = AE with onset or worsening in severity after first dose through last dose + 84 days (vutrisiran) or + 28 days (patisiran), or AE considered treatment-related at any time after first dose.
Unstratified relative risk (RR), odds ratio (OR), and risk difference (RD) were presented. In estimation of the OR and RR, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the RD.
[1] p-value based on the Wald test testing whether the relative risk equals to 1.
[2] p-value from a logistic regression using the penalized likelihood estimation (the FIRTH option) and with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Table 11.15
Treatment-Emergent Adverse Events: Subgroup Analysis of Overall Summary During the 18-Month Treatment Period
Safety Population

At least 1 severe AE

Subgroup Statistics	Vutrisiran (HELIOS-A) (N=122) n (%)	Patisiran (HELIOS-A) (N=42) n (%)
Region		
North America, n/N1 (%)	5/ 27 (18.5)	3/ 8 (37.5)
Risk difference (Vutrisiran - Patisiran), (95% CI)	-18.981 (-55.589, 17.626)	
Odds ratio (Vutrisiran/Patisiran), (95% CI)	0.379 (0.067, 2.136)	
Relative risk (Vutrisiran/Patisiran), (95% CI)	0.494 (0.150, 1.630)	
P-value [1]	0.2469	
Western Europe, n/N1 (%)	7/ 42 (16.7)	9/ 20 (45.0)
Risk difference (Vutrisiran - Patisiran), (95% CI)	-28.333 (-52.877, -3.789)	
Odds ratio (Vutrisiran/Patisiran), (95% CI)	0.244 (0.074, 0.810)	
Relative risk (Vutrisiran/Patisiran), (95% CI)	0.370 (0.161, 0.851)	
P-value [1]	0.0193	
Rest of World, n/N1 (%)	7/ 53 (13.2)	4/ 14 (28.6)
Risk difference (Vutrisiran - Patisiran), (95% CI)	-15.364 (-40.723, 9.995)	
Odds ratio (Vutrisiran/Patisiran), (95% CI)	0.380 (0.093, 1.552)	
Relative risk (Vutrisiran/Patisiran), (95% CI)	0.462 (0.157, 1.359)	
P-value [1]	0.1607	
P-value of Treatment*Region [2]	0.8899	

TEAE = Treatment-emergent adverse event = AE with onset or worsening in severity after first dose through last dose + 84 days (vutrisiran) or + 28 days (patisiran), or AE considered treatment-related at any time after first dose.
Unstratified relative risk (RR), odds ratio (OR), and risk difference (RD) were presented. In estimation of the OR and RR, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the RD.
[1] p-value based on the Wald test testing whether the relative risk equals to 1.
[2] p-value from a logistic regression using the penalized likelihood estimation (the FIRTH option) and with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Table 11.15
Treatment-Emergent Adverse Events: Subgroup Analysis of Overall Summary During the 18-Month Treatment Period
Safety Population

At least 1 severe AE

Subgroup Statistics	Vutrisiran (HELIOS-A) (N=122) n (%)	Patisiran (HELIOS-A) (N=42) n (%)
Baseline NIS		
<50, n/N1 (%)	11/ 78 (14.1)	11/ 27 (40.7)
Risk difference (Vutrisiran - Patisiran), (95% CI)	-26.638 (-46.717, -6.560)	
Odds ratio (Vutrisiran/Patisiran), (95% CI)	0.239 (0.088, 0.648)	
Relative risk (Vutrisiran/Patisiran), (95% CI)	0.346 (0.170, 0.705)	
P-value [1]	0.0035	
≥50, n/N1 (%)	8/ 44 (18.2)	5/ 15 (33.3)
Risk difference (Vutrisiran - Patisiran), (95% CI)	-15.152 (-41.590, 11.287)	
Odds ratio (Vutrisiran/Patisiran), (95% CI)	0.444 (0.119, 1.662)	
Relative risk (Vutrisiran/Patisiran), (95% CI)	0.545 (0.211, 1.412)	
P-value [1]	0.2118	
P-value of Treatment*Baseline NIS [2]	0.4746	

TEAE = Treatment-emergent adverse event = AE with onset or worsening in severity after first dose through last dose + 84 days (vutrisiran) or + 28 days (patisiran), or AE considered treatment-related at any time after first dose.
Unstratified relative risk (RR), odds ratio (OR), and risk difference (RD) were presented. In estimation of the OR and RR, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the RD.
[1] p-value based on the Wald test testing whether the relative risk equals to 1.
[2] p-value from a logistic regression using the penalized likelihood estimation (the FIRTH option) and with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Table 11.15
Treatment-Emergent Adverse Events: Subgroup Analysis of Overall Summary During the 18-Month Treatment Period
Safety Population

At least 1 severe AE

Subgroup Statistics	Vutrisiran (HELIOS-A) (N=122) n (%)	Patisiran (HELIOS-A) (N=42) n (%)
Previous Tetramer Stabilizer Use		
Yes, n/N1 (%)	7/ 75 (9.3)	13/ 33 (39.4)
Risk difference (Vutrisiran - Patisiran), (95% CI)	-30.061 (-47.985, -12.137)	
Odds ratio (Vutrisiran/Patisiran), (95% CI)	0.158 (0.056, 0.450)	
Relative risk (Vutrisiran/Patisiran), (95% CI)	0.237 (0.104, 0.539)	
P-value [1]	0.0006	
No, n/N1 (%)	12/ 47 (25.5)	3/ 9 (33.3)
Risk difference (Vutrisiran - Patisiran), (95% CI)	-7.801 (-41.027, 25.424)	
Odds ratio (Vutrisiran/Patisiran), (95% CI)	0.686 (0.148, 3.177)	
Relative risk (Vutrisiran/Patisiran), (95% CI)	0.766 (0.269, 2.178)	
P-value [1]	0.6170	
P-value of Treatment*Previous Tetramer Stabilizer Use [2]	0.1432	

TEAE = Treatment-emergent adverse event = AE with onset or worsening in severity after first dose through last dose + 84 days (vutrisiran) or + 28 days (patisiran), or AE considered treatment-related at any time after first dose.
Unstratified relative risk (RR), odds ratio (OR), and risk difference (RD) were presented. In estimation of the OR and RR, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the RD.
[1] p-value based on the Wald test testing whether the relative risk equals to 1.
[2] p-value from a logistic regression using the penalized likelihood estimation (the FIRTH option) and with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Table 11.15
Treatment-Emergent Adverse Events: Subgroup Analysis of Overall Summary During the 18-Month Treatment Period
Safety Population

At least 1 severe AE

Subgroup Statistics	Vutrisiran (HELIOS-A) (N=122) n (%)	Patisiran (HELIOS-A) (N=42) n (%)
Genotype		
V30M, n/N1 (%)	6/ 54 (11.1)	7/ 20 (35.0)
Risk difference (Vutrisiran - Patisiran), (95% CI)	-23.889 (-46.411, -1.367)	
Odds ratio (Vutrisiran/Patisiran), (95% CI)	0.232 (0.066, 0.811)	
Relative risk (Vutrisiran/Patisiran), (95% CI)	0.317 (0.121, 0.831)	
P-value [1]	0.0194	
non-V30M, n/N1 (%)	13/ 68 (19.1)	9/ 22 (40.9)
Risk difference (Vutrisiran - Patisiran), (95% CI)	-21.791 (-44.362, 0.780)	
Odds ratio (Vutrisiran/Patisiran), (95% CI)	0.341 (0.120, 0.969)	
Relative risk (Vutrisiran/Patisiran), (95% CI)	0.467 (0.232, 0.942)	
P-value [1]	0.0334	
P-value of Treatment*Genotype [2]	0.6619	

TEAE = Treatment-emergent adverse event = AE with onset or worsening in severity after first dose through last dose + 84 days (vutrisiran) or + 28 days (patisiran), or AE considered treatment-related at any time after first dose.
Unstratified relative risk (RR), odds ratio (OR), and risk difference (RD) were presented. In estimation of the OR and RR, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the RD.
[1] p-value based on the Wald test testing whether the relative risk equals to 1.
[2] p-value from a logistic regression using the penalized likelihood estimation (the FIRTH option) and with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Table 11.15
Treatment-Emergent Adverse Events: Subgroup Analysis of Overall Summary During the 18-Month Treatment Period
Safety Population

At least 1 severe AE

Subgroup Statistics	Vutrisiran (HELIOS-A) (N=122) n (%)	Patisiran (HELIOS-A) (N=42) n (%)
FAP Stage		
I, n/N1 (%)	11/ 84 (13.1)	12/ 31 (38.7)
Risk difference (Vutrisiran - Patisiran), (95% CI)	-25.614 (-44.217, -7.012)	
Odds ratio (Vutrisiran/Patisiran), (95% CI)	0.239 (0.091, 0.624)	
Relative risk (Vutrisiran/Patisiran), (95% CI)	0.338 (0.167, 0.686)	
P-value [1]	0.0027	
II&III, n/N1 (%)	8/ 38 (21.1)	4/ 11 (36.4)
Risk difference (Vutrisiran - Patisiran), (95% CI)	-15.311 (-46.554, 15.932)	
Odds ratio (Vutrisiran/Patisiran), (95% CI)	0.467 (0.109, 2.000)	
Relative risk (Vutrisiran/Patisiran), (95% CI)	0.579 (0.214, 1.566)	
P-value [1]	0.2817	
P-value of Treatment*FAP Stage [2]	0.4661	

TEAE = Treatment-emergent adverse event = AE with onset or worsening in severity after first dose through last dose + 84 days (vutrisiran) or + 28 days (patisiran), or AE considered treatment-related at any time after first dose.
Unstratified relative risk (RR), odds ratio (OR), and risk difference (RD) were presented. In estimation of the OR and RR, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the RD.
[1] p-value based on the Wald test testing whether the relative risk equals to 1.
[2] p-value from a logistic regression using the penalized likelihood estimation (the FIRTH option) and with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Table 11.15
Treatment-Emergent Adverse Events: Subgroup Analysis of Overall Summary During the 18-Month Treatment Period
Safety Population

At least 1 severe AE

Subgroup Statistics	Vutrisiran (HELIOS-A) (N=122) n (%)	Patisiran (HELIOS-A) (N=42) n (%)
Cardiac Subpopulation		
Yes, n/N1 (%)	9/ 40 (22.5)	5/ 14 (35.7)
Risk difference (Vutrisiran - Patisiran), (95% CI)	-13.214 (-41.453, 15.025)	
Odds ratio (Vutrisiran/Patisiran), (95% CI)	0.523 (0.139, 1.959)	
Relative risk (Vutrisiran/Patisiran), (95% CI)	0.630 (0.254, 1.562)	
P-value [1]	0.3187	
No, n/N1 (%)	10/ 82 (12.2)	11/ 28 (39.3)
Risk difference (Vutrisiran - Patisiran), (95% CI)	-27.091 (-46.517, -7.664)	
Odds ratio (Vutrisiran/Patisiran), (95% CI)	0.215 (0.078, 0.587)	
Relative risk (Vutrisiran/Patisiran), (95% CI)	0.310 (0.148, 0.651)	
P-value [1]	0.0020	
P-value of Treatment*Cardiac Subpopulation [2]	0.3065	

TEAE = Treatment-emergent adverse event = AE with onset or worsening in severity after first dose through last dose + 84 days (vutrisiran) or + 28 days (patisiran), or AE considered treatment-related at any time after first dose.
Unstratified relative risk (RR), odds ratio (OR), and risk difference (RD) were presented. In estimation of the OR and RR, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the RD.
[1] p-value based on the Wald test testing whether the relative risk equals to 1.
[2] p-value from a logistic regression using the penalized likelihood estimation (the FIRTH option) and with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Table 11.15
Treatment-Emergent Adverse Events: Subgroup Analysis of Overall Summary During the 18-Month Treatment Period
Safety Population

At least 1 severe AE

Subgroup Statistics	Vutrisiran (HELIOS-A) (N=122) n (%)	Patisiran (HELIOS-A) (N=42) n (%)
Weight (kg)		
<65 kg, n/N1 (%)	5/ 46 (10.9)	6/ 15 (40.0)
Risk difference (Vutrisiran - Patisiran), (95% CI)	-29.130 (-55.504, -2.757)	
Odds ratio (Vutrisiran/Patisiran), (95% CI)	0.183 (0.046, 0.734)	
Relative risk (Vutrisiran/Patisiran), (95% CI)	0.272 (0.097, 0.764)	
P-value [1]	0.0135	
>=65 kg, n/N1 (%)	14/ 76 (18.4)	10/ 27 (37.0)
Risk difference (Vutrisiran - Patisiran), (95% CI)	-18.616 (-38.809, 1.577)	
Odds ratio (Vutrisiran/Patisiran), (95% CI)	0.384 (0.145, 1.016)	
Relative risk (Vutrisiran/Patisiran), (95% CI)	0.497 (0.251, 0.984)	
P-value [1]	0.0449	
P-value of Treatment*Weight [2]	0.4188	

TEAE = Treatment-emergent adverse event = AE with onset or worsening in severity after first dose through last dose + 84 days (vutrisiran) or + 28 days (patisiran), or AE considered treatment-related at any time after first dose.
Unstratified relative risk (RR), odds ratio (OR), and risk difference (RD) were presented. In estimation of the OR and RR, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the RD.
[1] p-value based on the Wald test testing whether the relative risk equals to 1.
[2] p-value from a logistic regression using the penalized likelihood estimation (the FIRTH option) and with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Schwere UE nach SOC/PT

Schwere UE – SOC Infektionen und parasitäre Erkrankungen

Für diesen Endpunkt wurden für die Subgruppenmerkmale Alter, Geschlecht, Region, NIS zu Baseline, Vorherige Behandlung mit Tetramer-Stabilisatoren, Genotyp, FAP-Stadium, Kardiale Subpopulation und Gewicht weniger als zehn Ereignisse in den jeweiligen Subgruppenausprägungen berichtet. Daher werden, den Vorgaben des G-BA entsprechend, keine Subgruppenanalysen für diese Subgruppenmerkmale dargestellt.

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ALN-TTRSC02-002

Table 11.21
Severe Treatment-Emergent Adverse Events of Infections and Infestations (System Organ Class) during the 18-Month Treatment Period: Subgroup Analysis
Safety Population

Subgroup Statistics	Vutrisiran (HELIOS-A) (N=122) n (%)	Patisiran (HELIOS-A) (N=42) n (%)
Race		
White, n/N1 (%)	4/ 86 (4.7)	6/ 29 (20.7)
Risk difference (Vutrisiran - Patisiran), (95% CI)	-16.038 (-31.439, -0.638)	
Odds ratio (Vutrisiran/Patisiran), (95% CI)	0.187 (0.049, 0.719)	
Relative risk (Vutrisiran/Patisiran), (95% CI)	0.225 (0.068, 0.741)	
P-value [1]	0.0142	
All Other Races, n/N1 (%)	1/ 36 (2.8)	1/ 13 (7.7)
Risk difference (Vutrisiran - Patisiran), (95% CI)	-4.915 (-20.362, 10.533)	
Odds ratio (Vutrisiran/Patisiran), (95% CI)	0.343 (0.020, 5.917)	
Relative risk (Vutrisiran/Patisiran), (95% CI)	0.361 (0.024, 5.364)	
P-value [1]	0.4594	
P-value of Treatment*Race [2]	0.6787	

TEAE = Treatment-emergent adverse event = AE with onset or worsening in severity after first dose through last dose + 84 days (vutrisiran) or + 28 days (patisiran), or AE considered treatment-related at any time after first dose.
Unstratified relative risk (RR), odds ratio (OR), and risk difference (RD) were presented. In estimation of the OR and RR, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the RD.
[1] p-value based on the Wald test testing whether the relative risk equals to 1.
[2] p-value from a logistic regression using the penalized likelihood estimation (the FIRTH option) and with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Subgruppenanalysen zum Endpunkt „Schwerwiegende unerwünschte Ereignisse“

Gesamtrate SUE

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Table 11.15
Treatment-Emergent Adverse Events: Subgroup Analysis of Overall Summary During the 18-Month Treatment Period
Safety Population

At least 1 serious AE

Subgroup Statistics	Vutrisiran (HELIOS-A) (N=122) n (%)	Patisiran (HELIOS-A) (N=42) n (%)
Age (years)		
<65, n/N1 (%)	14/ 76 (18.4)	12/ 31 (38.7)
Risk difference (Vutrisiran - Patisiran), (95% CI)	-20.289 (-39.523, -1.054)	
Odds ratio (Vutrisiran/Patisiran), (95% CI)	0.358 (0.142, 0.903)	
Relative risk (Vutrisiran/Patisiran), (95% CI)	0.476 (0.249, 0.910)	
P-value [1]	0.0247	
≥65, n/N1 (%)	18/ 46 (39.1)	6/ 11 (54.5)
Risk difference (Vutrisiran - Patisiran), (95% CI)	-15.415 (-48.046, 17.216)	
Odds ratio (Vutrisiran/Patisiran), (95% CI)	0.536 (0.142, 2.018)	
Relative risk (Vutrisiran/Patisiran), (95% CI)	0.717 (0.375, 1.373)	
P-value [1]	0.3157	
P-value of Treatment*Age [2]	0.6125	

TEAE = Treatment-emergent adverse event = AE with onset or worsening in severity after first dose through last dose + 84 days (vutrisiran) or + 28 days (patisiran), or AE considered treatment-related at any time after first dose.
Unstratified relative risk (RR), odds ratio (OR), and risk difference (RD) were presented. In estimation of the OR and RR, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the RD.
[1] p-value based on the Wald test testing whether the relative risk equals to 1.
[2] p-value from a logistic regression using the penalized likelihood estimation (the FIRTH option) and with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Table 11.15
Treatment-Emergent Adverse Events: Subgroup Analysis of Overall Summary During the 18-Month Treatment Period
Safety Population

At least 1 serious AE

Subgroup Statistics	Vutrisiran (HELIOS-A) (N=122) n (%)	Patisiran (HELIOS-A) (N=42) n (%)
Sex		
Male, n/N1 (%)	20/ 79 (25.3)	9/ 27 (33.3)
Risk difference (Vutrisiran - Patisiran), (95% CI)	-8.017 (-28.219, 12.185)	
Odds ratio (Vutrisiran/Patisiran), (95% CI)	0.678 (0.263, 1.748)	
Relative risk (Vutrisiran/Patisiran), (95% CI)	0.759 (0.395, 1.461)	
P-value [1]	0.4098	
Female, n/N1 (%)	12/ 43 (27.9)	9/ 15 (60.0)
Risk difference (Vutrisiran - Patisiran), (95% CI)	-32.093 (-60.278, -3.908)	
Odds ratio (Vutrisiran/Patisiran), (95% CI)	0.258 (0.075, 0.882)	
Relative risk (Vutrisiran/Patisiran), (95% CI)	0.465 (0.247, 0.877)	
P-value [1]	0.0179	
P-value of Treatment*Sex [2]	0.2515	

TEAE = Treatment-emergent adverse event = AE with onset or worsening in severity after first dose through last dose + 84 days (vutrisiran) or + 28 days (patisiran), or AE considered treatment-related at any time after first dose.
Unstratified relative risk (RR), odds ratio (OR), and risk difference (RD) were presented. In estimation of the OR and RR, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the RD.
[1] p-value based on the Wald test testing whether the relative risk equals to 1.
[2] p-value from a logistic regression using the penalized likelihood estimation (the FIRTH option) and with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Table 11.15
Treatment-Emergent Adverse Events: Subgroup Analysis of Overall Summary During the 18-Month Treatment Period
Safety Population

At least 1 serious AE

Subgroup Statistics	Vutrisiran (HELIOS-A) (N=122) n (%)	Patisiran (HELIOS-A) (N=42) n (%)
Race		
White, n/N1 (%)	24/ 86 (27.9)	12/ 29 (41.4)
Risk difference (Vutrisiran - Patisiran), (95% CI)	-13.472 (-33.750, 6.805)	
Odds ratio (Vutrisiran/Patisiran), (95% CI)	0.548 (0.228, 1.317)	
Relative risk (Vutrisiran/Patisiran), (95% CI)	0.674 (0.389, 1.170)	
P-value [1]	0.1608	
All Other Races, n/N1 (%)	8/ 36 (22.2)	6/ 13 (46.2)
Risk difference (Vutrisiran - Patisiran), (95% CI)	-23.932 (-54.243, 6.380)	
Odds ratio (Vutrisiran/Patisiran), (95% CI)	0.333 (0.087, 1.278)	
Relative risk (Vutrisiran/Patisiran), (95% CI)	0.481 (0.206, 1.124)	
P-value [1]	0.0910	
P-value of Treatment*Race [2]	0.5673	

TEAE = Treatment-emergent adverse event = AE with onset or worsening in severity after first dose through last dose + 84 days (vutrisiran) or + 28 days (patisiran), or AE considered treatment-related at any time after first dose.
Unstratified relative risk (RR), odds ratio (OR), and risk difference (RD) were presented. In estimation of the OR and RR, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the RD.
[1] p-value based on the Wald test testing whether the relative risk equals to 1.
[2] p-value from a logistic regression using the penalized likelihood estimation (the FIRTH option) and with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Table 11.15
Treatment-Emergent Adverse Events: Subgroup Analysis of Overall Summary During the 18-Month Treatment Period
Safety Population

At least 1 serious AE

Subgroup Statistics	Vutrisiran (HELIOS-A) (N=122) n (%)	Patisiran (HELIOS-A) (N=42) n (%)
Region		
North America, n/N1 (%)	8/ 27 (29.6)	3/ 8 (37.5)
Risk difference (Vutrisiran - Patisiran), (95% CI)	-7.870 (-45.581, 29.840)	
Odds ratio (Vutrisiran/Patisiran), (95% CI)	0.702 (0.134, 3.664)	
Relative risk (Vutrisiran/Patisiran), (95% CI)	0.790 (0.272, 2.296)	
P-value [1]	0.6652	
Western Europe, n/N1 (%)	11/ 42 (26.2)	10/ 20 (50.0)
Risk difference (Vutrisiran - Patisiran), (95% CI)	-23.810 (-49.441, 1.822)	
Odds ratio (Vutrisiran/Patisiran), (95% CI)	0.355 (0.116, 1.081)	
Relative risk (Vutrisiran/Patisiran), (95% CI)	0.524 (0.268, 1.024)	
P-value [1]	0.0588	
Rest of World, n/N1 (%)	13/ 53 (24.5)	5/ 14 (35.7)
Risk difference (Vutrisiran - Patisiran), (95% CI)	-11.186 (-38.829, 16.457)	
Odds ratio (Vutrisiran/Patisiran), (95% CI)	0.585 (0.166, 2.062)	
Relative risk (Vutrisiran/Patisiran), (95% CI)	0.687 (0.295, 1.602)	
P-value [1]	0.3845	
P-value of Treatment*Region [2]	0.7815	

TEAE = Treatment-emergent adverse event = AE with onset or worsening in severity after first dose through last dose + 84 days (vutrisiran) or + 28 days (patisiran), or AE considered treatment-related at any time after first dose.
Unstratified relative risk (RR), odds ratio (OR), and risk difference (RD) were presented. In estimation of the OR and RR, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the RD.
[1] p-value based on the Wald test testing whether the relative risk equals to 1.
[2] p-value from a logistic regression using the penalized likelihood estimation (the FIRTH option) and with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Table 11.15
Treatment-Emergent Adverse Events: Subgroup Analysis of Overall Summary During the 18-Month Treatment Period
Safety Population

At least 1 serious AE

Subgroup Statistics	Vutrisiran (HELIOS-A) (N=122) n (%)	Patisiran (HELIOS-A) (N=42) n (%)
Baseline NIS		
<50, n/N1 (%)	18/ 78 (23.1)	12/ 27 (44.4)
Risk difference (Vutrisiran - Patisiran), (95% CI)	-21.368 (-42.313, -0.422)	
Odds ratio (Vutrisiran/Patisiran), (95% CI)	0.375 (0.149, 0.945)	
Relative risk (Vutrisiran/Patisiran), (95% CI)	0.519 (0.289, 0.932)	
P-value [1]	0.0281	
≥50, n/N1 (%)	14/ 44 (31.8)	6/ 15 (40.0)
Risk difference (Vutrisiran - Patisiran), (95% CI)	-8.182 (-36.537, 20.174)	
Odds ratio (Vutrisiran/Patisiran), (95% CI)	0.700 (0.208, 2.353)	
Relative risk (Vutrisiran/Patisiran), (95% CI)	0.795 (0.374, 1.694)	
P-value [1]	0.5529	
P-value of Treatment*Baseline NIS [2]	0.4351	

TEAE = Treatment-emergent adverse event = AE with onset or worsening in severity after first dose through last dose + 84 days (vutrisiran) or + 28 days (patisiran), or AE considered treatment-related at any time after first dose.
Unstratified relative risk (RR), odds ratio (OR), and risk difference (RD) were presented. In estimation of the OR and RR, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the RD.
[1] p-value based on the Wald test testing whether the relative risk equals to 1.
[2] p-value from a logistic regression using the penalized likelihood estimation (the FIRTH option) and with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Table 11.15
Treatment-Emergent Adverse Events: Subgroup Analysis of Overall Summary During the 18-Month Treatment Period
Safety Population

At least 1 serious AE

Subgroup Statistics	Vutrisiran (HELIOS-A) (N=122) n (%)	Patisiran (HELIOS-A) (N=42) n (%)
Previous Tetramer Stabilizer Use		
Yes, n/N1 (%)	15/ 75 (20.0)	14/ 33 (42.4)
Risk difference (Vutrisiran - Patisiran), (95% CI)	-22.424 (-41.563, -3.286)	
Odds ratio (Vutrisiran/Patisiran), (95% CI)	0.339 (0.139, 0.828)	
Relative risk (Vutrisiran/Patisiran), (95% CI)	0.471 (0.258, 0.861)	
P-value [1]	0.0144	
No, n/N1 (%)	17/ 47 (36.2)	4/ 9 (44.4)
Risk difference (Vutrisiran - Patisiran), (95% CI)	-8.274 (-43.525, 26.976)	
Odds ratio (Vutrisiran/Patisiran), (95% CI)	0.708 (0.167, 2.999)	
Relative risk (Vutrisiran/Patisiran), (95% CI)	0.814 (0.357, 1.854)	
P-value [1]	0.6238	
P-value of Treatment*Previous Tetramer Stabilizer Use [2]	0.4107	

TEAE = Treatment-emergent adverse event = AE with onset or worsening in severity after first dose through last dose + 84 days (vutrisiran) or + 28 days (patisiran), or AE considered treatment-related at any time after first dose.
Unstratified relative risk (RR), odds ratio (OR), and risk difference (RD) were presented. In estimation of the OR and RR, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the RD.
[1] p-value based on the Wald test testing whether the relative risk equals to 1.
[2] p-value from a logistic regression using the penalized likelihood estimation (the FIRTH option) and with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Table 11.15
Treatment-Emergent Adverse Events: Subgroup Analysis of Overall Summary During the 18-Month Treatment Period
Safety Population

At least 1 serious AE

Subgroup Statistics	Vutrisiran (HELIOS-A) (N=122) n (%)	Patisiran (HELIOS-A) (N=42) n (%)
Genotype		
V30M, n/N1 (%)	10/ 54 (18.5)	8/ 20 (40.0)
Risk difference (Vutrisiran - Patisiran), (95% CI)	-21.481 (-45.321, 2.358)	
Odds ratio (Vutrisiran/Patisiran), (95% CI)	0.341 (0.110, 1.053)	
Relative risk (Vutrisiran/Patisiran), (95% CI)	0.463 (0.213, 1.005)	
P-value [1]	0.0516	
non-V30M, n/N1 (%)	22/ 68 (32.4)	10/ 22 (45.5)
Risk difference (Vutrisiran - Patisiran), (95% CI)	-13.102 (-36.693, 10.490)	
Odds ratio (Vutrisiran/Patisiran), (95% CI)	0.574 (0.215, 1.531)	
Relative risk (Vutrisiran/Patisiran), (95% CI)	0.712 (0.402, 1.262)	
P-value [1]	0.2443	
P-value of Treatment*Genotype [2]	0.5048	

TEAE = Treatment-emergent adverse event = AE with onset or worsening in severity after first dose through last dose + 84 days (vutrisiran) or + 28 days (patisiran), or AE considered treatment-related at any time after first dose.
Unstratified relative risk (RR), odds ratio (OR), and risk difference (RD) were presented. In estimation of the OR and RR, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the RD.
[1] p-value based on the Wald test testing whether the relative risk equals to 1.
[2] p-value from a logistic regression using the penalized likelihood estimation (the FIRTH option) and with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Table 11.15
Treatment-Emergent Adverse Events: Subgroup Analysis of Overall Summary During the 18-Month Treatment Period
Safety Population

At least 1 serious AE

Subgroup Statistics	Vutrisiran (HELIOS-A) (N=122) n (%)	Patisiran (HELIOS-A) (N=42) n (%)
FAP Stage		
I, n/N1 (%)	17/ 84 (20.2)	12/ 31 (38.7)
Risk difference (Vutrisiran - Patisiran), (95% CI)	-18.472 (-37.650, 0.707)	
Odds ratio (Vutrisiran/Patisiran), (95% CI)	0.402 (0.164, 0.986)	
Relative risk (Vutrisiran/Patisiran), (95% CI)	0.523 (0.283, 0.966)	
P-value [1]	0.0383	
II&III, n/N1 (%)	15/ 38 (39.5)	6/ 11 (54.5)
Risk difference (Vutrisiran - Patisiran), (95% CI)	-15.072 (-48.349, 18.205)	
Odds ratio (Vutrisiran/Patisiran), (95% CI)	0.543 (0.140, 2.104)	
Relative risk (Vutrisiran/Patisiran), (95% CI)	0.724 (0.371, 1.411)	
P-value [1]	0.3426	
P-value of Treatment*FAP Stage [2]	0.6969	

TEAE = Treatment-emergent adverse event = AE with onset or worsening in severity after first dose through last dose + 84 days (vutrisiran) or + 28 days (patisiran), or AE considered treatment-related at any time after first dose.
Unstratified relative risk (RR), odds ratio (OR), and risk difference (RD) were presented. In estimation of the OR and RR, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the RD.
[1] p-value based on the Wald test testing whether the relative risk equals to 1.
[2] p-value from a logistic regression using the penalized likelihood estimation (the FIRTH option) and with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Table 11.15
Treatment-Emergent Adverse Events: Subgroup Analysis of Overall Summary During the 18-Month Treatment Period
Safety Population

At least 1 serious AE

Subgroup Statistics	Vutrisiran (HELIOS-A) (N=122) n (%)	Patisiran (HELIOS-A) (N=42) n (%)
Cardiac Subpopulation		
Yes, n/N1 (%)	13/ 40 (32.5)	5/ 14 (35.7)
Risk difference (Vutrisiran - Patisiran), (95% CI)	-3.214 (-32.208, 25.780)	
Odds ratio (Vutrisiran/Patisiran), (95% CI)	0.867 (0.241, 3.110)	
Relative risk (Vutrisiran/Patisiran), (95% CI)	0.910 (0.396, 2.093)	
P-value [1]	0.8243	
No, n/N1 (%)	19/ 82 (23.2)	13/ 28 (46.4)
Risk difference (Vutrisiran - Patisiran), (95% CI)	-23.258 (-43.864, -2.651)	
Odds ratio (Vutrisiran/Patisiran), (95% CI)	0.348 (0.141, 0.858)	
Relative risk (Vutrisiran/Patisiran), (95% CI)	0.499 (0.285, 0.874)	
P-value [1]	0.0150	
P-value of Treatment*Cardiac Subpopulation [2]	0.2697	

TEAE = Treatment-emergent adverse event = AE with onset or worsening in severity after first dose through last dose + 84 days (vutrisiran) or + 28 days (patisiran), or AE considered treatment-related at any time after first dose.
Unstratified relative risk (RR), odds ratio (OR), and risk difference (RD) were presented. In estimation of the OR and RR, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the RD.
[1] p-value based on the Wald test testing whether the relative risk equals to 1.
[2] p-value from a logistic regression using the penalized likelihood estimation (the FIRTH option) and with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Table 11.15
Treatment-Emergent Adverse Events: Subgroup Analysis of Overall Summary During the 18-Month Treatment Period
Safety Population

At least 1 serious AE

Subgroup Statistics	Vutrisiran (HELIOS-A) (N=122) n (%)	Patisiran (HELIOS-A) (N=42) n (%)
Weight (kg)		
<65 kg, n/N1 (%)	10/ 46 (21.7)	9/ 15 (60.0)
Risk difference (Vutrisiran - Patisiran), (95% CI)	-38.261 (-65.769, -10.752)	
Odds ratio (Vutrisiran/Patisiran), (95% CI)	0.185 (0.053, 0.645)	
Relative risk (Vutrisiran/Patisiran), (95% CI)	0.362 (0.182, 0.720)	
P-value [1]	0.0038	
>=65 kg, n/N1 (%)	22/ 76 (28.9)	9/ 27 (33.3)
Risk difference (Vutrisiran - Patisiran), (95% CI)	-4.386 (-24.883, 16.111)	
Odds ratio (Vutrisiran/Patisiran), (95% CI)	0.815 (0.318, 2.089)	
Relative risk (Vutrisiran/Patisiran), (95% CI)	0.868 (0.458, 1.646)	
P-value [1]	0.6653	
P-value of Treatment*Weight [2]	0.0764	

TEAE = Treatment-emergent adverse event = AE with onset or worsening in severity after first dose through last dose + 84 days (vutrisiran) or + 28 days (patisiran), or AE considered treatment-related at any time after first dose.
Unstratified relative risk (RR), odds ratio (OR), and risk difference (RD) were presented. In estimation of the OR and RR, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the RD.
[1] p-value based on the Wald test testing whether the relative risk equals to 1.
[2] p-value from a logistic regression using the penalized likelihood estimation (the FIRTH option) and with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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SUE nach SOC/PT

SUE – SOC Erkrankungen des Immunsystems

Für diesen Endpunkt wurden insgesamt weniger als zehn Ereignisse auf Ebene der Gesamtpopulation berichtet. Daher werden, den Vorgaben des G-BA entsprechend, keine Subgruppenanalysen für diesen Endpunkt dargestellt.

SUE – PT Reaktion im Zusammenhang mit einer Infusion

Für diesen Endpunkt wurden insgesamt weniger als zehn Ereignisse auf Ebene der Gesamtpopulation berichtet. Daher werden, den Vorgaben des G-BA entsprechend, keine Subgruppenanalysen für diesen Endpunkt dargestellt.

SUE – PT Zellulitis an der Infusionsstelle

Für diesen Endpunkt wurden insgesamt weniger als zehn Ereignisse auf Ebene der Gesamtpopulation berichtet. Daher werden, den Vorgaben des G-BA entsprechend, keine Subgruppenanalysen für diesen Endpunkt dargestellt.

SUE – SOC Infektionen und parasitäre Erkrankungen

Für diesen Endpunkt wurden für die Subgruppenmerkmale Alter und Genotyp weniger als zehn Ereignisse in den jeweiligen Subgruppenausprägungen berichtet. Daher werden, den Vorgaben des G-BA entsprechend, keine Subgruppenanalysen für diese Subgruppenmerkmale dargestellt.

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Table 11.22
Serious Treatment-Emergent Adverse Events of Infections and Infestations (System Organ Class) during the 18-Month Treatment Period: Subgroup Analysis
Safety Population

Subgroup Statistics	Vutrisiran (HELIOS-A) (N=122) n (%)	Patisiran (HELIOS-A) (N=42) n (%)
Sex		
Male, n/N1 (%)	7/ 79 (8.9)	3/ 27 (11.1)
Risk difference (Vutrisiran - Patisiran), (95% CI)	-2.250 (-15.659, 11.158)	
Odds ratio (Vutrisiran/Patisiran), (95% CI)	0.778 (0.186, 3.248)	
Relative risk (Vutrisiran/Patisiran), (95% CI)	0.797 (0.222, 2.868)	
P-value [1]	0.7289	
Female, n/N1 (%)	2/ 43 (4.7)	5/ 15 (33.3)
Risk difference (Vutrisiran - Patisiran), (95% CI)	-28.682 (-53.355, -4.010)	
Odds ratio (Vutrisiran/Patisiran), (95% CI)	0.098 (0.016, 0.578)	
Relative risk (Vutrisiran/Patisiran), (95% CI)	0.140 (0.030, 0.645)	
P-value [1]	0.0117	
P-value of Treatment*Sex [2]	0.0953	

TEAE = Treatment-emergent adverse event = AE with onset or worsening in severity after first dose through last dose + 84 days (vutrisiran) or + 28 days (patisiran), or AE considered treatment-related at any time after first dose.
Unstratified relative risk (RR), odds ratio (OR), and risk difference (RD) were presented. In estimation of the OR and RR, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the RD.
[1] p-value based on the Wald test testing whether the relative risk equals to 1.
[2] p-value from a logistic regression using the penalized likelihood estimation (the FIRTH option) and with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Table 11.22
Serious Treatment-Emergent Adverse Events of Infections and Infestations (System Organ Class) during the 18-Month Treatment Period: Subgroup Analysis
Safety Population

Subgroup Statistics	Vutrisiran (HELIOS-A) (N=122) n (%)	Patisiran (HELIOS-A) (N=42) n (%)
Race		
White, n/N1 (%)	7/ 86 (8.1)	6/ 29 (20.7)
Risk difference (Vutrisiran - Patisiran), (95% CI)	-12.550 (-28.385, 3.285)	
Odds ratio (Vutrisiran/Patisiran), (95% CI)	0.340 (0.104, 1.111)	
Relative risk (Vutrisiran/Patisiran), (95% CI)	0.393 (0.144, 1.076)	
P-value [1]	0.0691	
All Other Races, n/N1 (%)	2/ 36 (5.6)	2/ 13 (15.4)
Risk difference (Vutrisiran - Patisiran), (95% CI)	-9.829 (-30.821, 11.163)	
Odds ratio (Vutrisiran/Patisiran), (95% CI)	0.324 (0.041, 2.576)	
Relative risk (Vutrisiran/Patisiran), (95% CI)	0.361 (0.057, 2.307)	
P-value [1]	0.2817	
P-value of Treatment*Race [2]	0.9841	

TEAE = Treatment-emergent adverse event = AE with onset or worsening in severity after first dose through last dose + 84 days (vutrisiran) or + 28 days (patisiran), or AE considered treatment-related at any time after first dose.
Unstratified relative risk (RR), odds ratio (OR), and risk difference (RD) were presented. In estimation of the OR and RR, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the RD.
[1] p-value based on the Wald test testing whether the relative risk equals to 1.
[2] p-value from a logistic regression using the penalized likelihood estimation (the FIRTH option) and with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Table 11.22
Serious Treatment-Emergent Adverse Events of Infections and Infestations (System Organ Class) during the 18-Month Treatment Period: Subgroup Analysis
Safety Population

Subgroup Statistics	Vutrisiran (HELIOS-A) (N=122) n (%)	Patisiran (HELIOS-A) (N=42) n (%)
Region		
North America, n/N1 (%)	4/ 27 (14.8)	1/ 8 (12.5)
Risk difference (Vutrisiran - Patisiran), (95% CI)	2.315 (-24.232, 28.862)	
Odds ratio (Vutrisiran/Patisiran), (95% CI)	1.217 (0.116, 12.752)	
Relative risk (Vutrisiran/Patisiran), (95% CI)	1.185 (0.153, 9.155)	
P-value [1]	0.8706	
Western Europe, n/N1 (%)	5/ 42 (11.9)	5/ 20 (25.0)
Risk difference (Vutrisiran - Patisiran), (95% CI)	-13.095 (-34.451, 8.260)	
Odds ratio (Vutrisiran/Patisiran), (95% CI)	0.405 (0.102, 1.607)	
Relative risk (Vutrisiran/Patisiran), (95% CI)	0.476 (0.155, 1.459)	
P-value [1]	0.1939	
Rest of World, n/N1 (%)	0/ 53 (0)	2/ 14 (14.3)
Risk difference (Vutrisiran - Patisiran), (95% CI)	-14.286 (-32.616, 4.044)	
Odds ratio (Vutrisiran/Patisiran), (95% CI)	0.047 (0.002, 1.035)	
Relative risk (Vutrisiran/Patisiran), (95% CI)	0.056 (0.003, 1.096)	
P-value [1]	0.0575	
P-value of Treatment*Region [2]	0.2947	

TEAE = Treatment-emergent adverse event = AE with onset or worsening in severity after first dose through last dose + 84 days (vutrisiran) or + 28 days (patisiran), or AE considered treatment-related at any time after first dose.
Unstratified relative risk (RR), odds ratio (OR), and risk difference (RD) were presented. In estimation of the OR and RR, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the RD.
[1] p-value based on the Wald test testing whether the relative risk equals to 1.
[2] p-value from a logistic regression using the penalized likelihood estimation (the FIRTH option) and with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Table 11.22
Serious Treatment-Emergent Adverse Events of Infections and Infestations (System Organ Class) during the 18-Month Treatment Period: Subgroup Analysis
Safety Population

Subgroup Statistics	Vutrisiran (HELIOS-A) (N=122) n (%)	Patisiran (HELIOS-A) (N=42) n (%)
Baseline NIS		
<50, n/N1 (%)	5/ 78 (6.4)	6/ 27 (22.2)
Risk difference (Vutrisiran - Patisiran), (95% CI)	-15.812 (-32.409, 0.785)	
Odds ratio (Vutrisiran/Patisiran), (95% CI)	0.240 (0.067, 0.864)	
Relative risk (Vutrisiran/Patisiran), (95% CI)	0.288 (0.096, 0.869)	
P-value [1]	0.0272	
≥50, n/N1 (%)	4/ 44 (9.1)	2/ 15 (13.3)
Risk difference (Vutrisiran - Patisiran), (95% CI)	-4.242 (-23.428, 14.943)	
Odds ratio (Vutrisiran/Patisiran), (95% CI)	0.650 (0.106, 3.968)	
Relative risk (Vutrisiran/Patisiran), (95% CI)	0.682 (0.139, 3.354)	
P-value [1]	0.6375	
P-value of Treatment*Baseline NIS [2]	0.4118	

TEAE = Treatment-emergent adverse event = AE with onset or worsening in severity after first dose through last dose + 84 days (vutrisiran) or + 28 days (patisiran), or AE considered treatment-related at any time after first dose.
Unstratified relative risk (RR), odds ratio (OR), and risk difference (RD) were presented. In estimation of the OR and RR, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the RD.
[1] p-value based on the Wald test testing whether the relative risk equals to 1.
[2] p-value from a logistic regression using the penalized likelihood estimation (the FIRTH option) and with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Table 11.22
Serious Treatment-Emergent Adverse Events of Infections and Infestations (System Organ Class) during the 18-Month Treatment Period: Subgroup Analysis
Safety Population

Subgroup Statistics	Vutrisiran (HELIOS-A) (N=122) n (%)	Patisiran (HELIOS-A) (N=42) n (%)
Previous Tetramer Stabilizer Use		
Yes, n/N1 (%)	2/ 75 (2.7)	8/ 33 (24.2)
Risk difference (Vutrisiran - Patisiran), (95% CI)	-21.576 (-36.645, -6.506)	
Odds ratio (Vutrisiran/Patisiran), (95% CI)	0.086 (0.017, 0.430)	
Relative risk (Vutrisiran/Patisiran), (95% CI)	0.110 (0.025, 0.490)	
P-value [1]	0.0038	
No, n/N1 (%)	7/ 47 (14.9)	0/ 9 (0)
Risk difference (Vutrisiran - Patisiran), (95% CI)	14.894 (4.715, 25.072)	
Odds ratio (Vutrisiran/Patisiran), (95% CI)	3.519 (0.184, 67.132)	
Relative risk (Vutrisiran/Patisiran), (95% CI)	3.125 (0.194, 50.395)	
P-value [1]	0.4219	
P-value of Treatment*Previous Tetramer Stabilizer Use [2]	0.0437	

TEAE = Treatment-emergent adverse event = AE with onset or worsening in severity after first dose through last dose + 84 days (vutrisiran) or + 28 days (patisiran), or AE considered treatment-related at any time after first dose.
Unstratified relative risk (RR), odds ratio (OR), and risk difference (RD) were presented. In estimation of the OR and RR, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the RD.
[1] p-value based on the Wald test testing whether the relative risk equals to 1.
[2] p-value from a logistic regression using the penalized likelihood estimation (the FIRTH option) and with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Table 11.22
Serious Treatment-Emergent Adverse Events of Infections and Infestations (System Organ Class) during the 18-Month Treatment Period: Subgroup Analysis
Safety Population

Subgroup Statistics	Vutrisiran (HELIOS-A) (N=122) n (%)	Patisiran (HELIOS-A) (N=42) n (%)
FAP Stage		
I, n/N1 (%)	4/ 84 (4.8)	6/ 31 (19.4)
Risk difference (Vutrisiran - Patisiran), (95% CI)	-14.593 (-29.227, 0.041)	
Odds ratio (Vutrisiran/Patisiran), (95% CI)	0.208 (0.054, 0.798)	
Relative risk (Vutrisiran/Patisiran), (95% CI)	0.246 (0.074, 0.814)	
P-value [1]	0.0216	
II&III, n/N1 (%)	5/ 38 (13.2)	2/ 11 (18.2)
Risk difference (Vutrisiran - Patisiran), (95% CI)	-5.024 (-30.224, 20.176)	
Odds ratio (Vutrisiran/Patisiran), (95% CI)	0.682 (0.113, 4.116)	
Relative risk (Vutrisiran/Patisiran), (95% CI)	0.724 (0.162, 3.231)	
P-value [1]	0.6718	
P-value of Treatment*FAP Stage [2]	0.3411	

TEAE = Treatment-emergent adverse event = AE with onset or worsening in severity after first dose through last dose + 84 days (vutrisiran) or + 28 days (patisiran), or AE considered treatment-related at any time after first dose.
Unstratified relative risk (RR), odds ratio (OR), and risk difference (RD) were presented. In estimation of the OR and RR, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the RD.
[1] p-value based on the Wald test testing whether the relative risk equals to 1.
[2] p-value from a logistic regression using the penalized likelihood estimation (the FIRTH option) and with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Table 11.22
Serious Treatment-Emergent Adverse Events of Infections and Infestations (System Organ Class) during the 18-Month Treatment Period: Subgroup Analysis
Safety Population

Subgroup Statistics	Vutrisiran (HELIOS-A) (N=122) n (%)	Patisiran (HELIOS-A) (N=42) n (%)
Cardiac Subpopulation		
Yes, n/N1 (%)	4/ 40 (10.0)	1/ 14 (7.1)
Risk difference (Vutrisiran - Patisiran), (95% CI)	2.857 (-13.527, 19.241)	
Odds ratio (Vutrisiran/Patisiran), (95% CI)	1.444 (0.148, 14.139)	
Relative risk (Vutrisiran/Patisiran), (95% CI)	1.400 (0.171, 11.491)	
P-value [1]	0.7541	
No, n/N1 (%)	5/ 82 (6.1)	7/ 28 (25.0)
Risk difference (Vutrisiran - Patisiran), (95% CI)	-18.902 (-35.757, -2.048)	
Odds ratio (Vutrisiran/Patisiran), (95% CI)	0.195 (0.056, 0.677)	
Relative risk (Vutrisiran/Patisiran), (95% CI)	0.244 (0.084, 0.707)	
P-value [1]	0.0094	
P-value of Treatment*Cardiac Subpopulation [2]	0.1564	

TEAE = Treatment-emergent adverse event = AE with onset or worsening in severity after first dose through last dose + 84 days (vutrisiran) or + 28 days (patisiran), or AE considered treatment-related at any time after first dose.
Unstratified relative risk (RR), odds ratio (OR), and risk difference (RD) were presented. In estimation of the OR and RR, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the RD.
[1] p-value based on the Wald test testing whether the relative risk equals to 1.
[2] p-value from a logistic regression using the penalized likelihood estimation (the FIRTH option) and with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Table 11.22
Serious Treatment-Emergent Adverse Events of Infections and Infestations (System Organ Class) during the 18-Month Treatment Period: Subgroup Analysis
Safety Population

Subgroup Statistics	Vutrisiran (HELIOS-A) (N=122) n (%)	Patisiran (HELIOS-A) (N=42) n (%)
Weight (kg)		
<65 kg, n/N1 (%)	2/ 46 (4.3)	5/ 15 (33.3)
Risk difference (Vutrisiran - Patisiran), (95% CI)	-28.986 (-53.559, -4.412)	
Odds ratio (Vutrisiran/Patisiran), (95% CI)	0.091 (0.015, 0.538)	
Relative risk (Vutrisiran/Patisiran), (95% CI)	0.130 (0.028, 0.604)	
P-value [1]	0.0092	
>=65 kg, n/N1 (%)	7/ 76 (9.2)	3/ 27 (11.1)
Risk difference (Vutrisiran - Patisiran), (95% CI)	-1.901 (-15.420, 11.619)	
Odds ratio (Vutrisiran/Patisiran), (95% CI)	0.812 (0.194, 3.392)	
Relative risk (Vutrisiran/Patisiran), (95% CI)	0.829 (0.231, 2.979)	
P-value [1]	0.7738	
P-value of Treatment*Weight [2]	0.0766	

TEAE = Treatment-emergent adverse event = AE with onset or worsening in severity after first dose through last dose + 84 days (vutrisiran) or + 28 days (patisiran), or AE considered treatment-related at any time after first dose.
Unstratified relative risk (RR), odds ratio (OR), and risk difference (RD) were presented. In estimation of the OR and RR, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the RD.
[1] p-value based on the Wald test testing whether the relative risk equals to 1.
[2] p-value from a logistic regression using the penalized likelihood estimation (the FIRTH option) and with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Todesfälle

Für diesen Endpunkt wurden insgesamt weniger als zehn Ereignisse auf Ebene der Gesamtpopulation berichtet. Daher werden, den Vorgaben des G-BA entsprechend, keine Subgruppenanalysen für diesen Endpunkt dargestellt.

Subgruppenanalysen zum Endpunkt „Unerwünschte Ereignisse, die zum Therapieabbruch führten“

Für diesen Endpunkt wurden insgesamt weniger als zehn Ereignisse auf Ebene der Gesamtpopulation berichtet. Daher werden, den Vorgaben des G-BA entsprechend, keine Subgruppenanalysen für diesen Endpunkt dargestellt.

Subgruppenanalysen zum Endpunkt „Unerwünschte Ereignisse von speziellem Interesse, differenziert nach Schweregrad“

Durch Arzneimittel bedingte Erkrankungen der Leber

Durch Arzneimittel bedingte Erkrankungen der Leber – Ereignisse jeglichen Schweregrades

Für diesen Endpunkt wurden für die Subgruppenmerkmale Alter, Geschlecht, Abstammung, Region, Vorherige Behandlung mit Tetramer-Stabilisatoren, Genotyp, Kardiale Subpopulation und Gewicht weniger als zehn Ereignisse in den jeweiligen Subgruppenausprägungen berichtet. Daher werden, den Vorgaben des G-BA entsprechend, keine Subgruppenanalysen für diese Subgruppenmerkmale dargestellt.

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Table 11.27
Treatment-Emergent Adverse Events Mapped to Drug-related Hepatic Disorders - Comprehensive Search SMQ:
Incidence by System Organ Class and Preferred Term During the 18-Month Treatment Period: Subgroup Analysis
Safety Population

At least 1 AE

Subgroup Statistics	Vutrisiran (HELIOS-A) (N=122) n (%)	Patisiran (HELIOS-A) (N=42) n (%)
Baseline NIS		
<50, n/N1 (%)	5/ 78 (6.4)	5/ 27 (18.5)
Risk difference (Vutrisiran - Patisiran), (95% CI)	-12.108 (-27.736, 3.520)	
Odds ratio (Vutrisiran/Patisiran), (95% CI)	0.301 (0.080, 1.137)	
Relative risk (Vutrisiran/Patisiran), (95% CI)	0.346 (0.109, 1.104)	
P-value [1]	0.0730	
≥50, n/N1 (%)	1/ 44 (2.3)	1/ 15 (6.7)
Risk difference (Vutrisiran - Patisiran), (95% CI)	-4.394 (-17.763, 8.975)	
Odds ratio (Vutrisiran/Patisiran), (95% CI)	0.326 (0.019, 5.554)	
Relative risk (Vutrisiran/Patisiran), (95% CI)	0.341 (0.023, 5.119)	
P-value [1]	0.4362	
P-value of Treatment*Baseline NIS [2]	0.9510	

TEAE = Treatment-emergent adverse event = AE with onset or worsening in severity after first dose through last dose + 84 days (vutrisiran) or + 28 days (patisiran), or AE considered treatment-related at any time after first dose.
Missing severity/relationship imputed to severe/related, respectively.
Unstratified relative risk (RR), odds ratio (OR), and risk difference (RD) were presented. In estimation of the OR and RR, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the RD.
[1] p-value based on the Wald test testing whether the relative risk equals to 1.
[2] p-value from a logistic regression using the penalized likelihood estimation (the FIRTH option) and with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Table 11.27
Treatment-Emergent Adverse Events Mapped to Drug-related Hepatic Disorders - Comprehensive Search SMQ:
Incidence by System Organ Class and Preferred Term During the 18-Month Treatment Period: Subgroup Analysis
Safety Population

At least 1 AE

Subgroup Statistics	Vutrisiran (HELIOS-A) (N=122) n (%)	Patisiran (HELIOS-A) (N=42) n (%)
FAP Stage		
I, n/N1 (%)	5/ 84 (6.0)	5/ 31 (16.1)
Risk difference (Vutrisiran - Patisiran), (95% CI)	-10.177 (-24.077, 3.724)	
Odds ratio (Vutrisiran/Patisiran), (95% CI)	0.329 (0.088, 1.228)	
Relative risk (Vutrisiran/Patisiran), (95% CI)	0.369 (0.115, 1.188)	
P-value [1]	0.0947	
II&III, n/N1 (%)	1/ 38 (2.6)	1/ 11 (9.1)
Risk difference (Vutrisiran - Patisiran), (95% CI)	-6.459 (-24.194, 11.275)	
Odds ratio (Vutrisiran/Patisiran), (95% CI)	0.270 (0.016, 4.712)	
Relative risk (Vutrisiran/Patisiran), (95% CI)	0.289 (0.020, 4.262)	
P-value [1]	0.3663	
P-value of Treatment*FAP Stage [2]	0.9011	

TEAE = Treatment-emergent adverse event = AE with onset or worsening in severity after first dose through last dose + 84 days (vutrisiran) or + 28 days (patisiran), or AE considered treatment-related at any time after first dose.
Missing severity/relationship imputed to severe/related, respectively.
Unstratified relative risk (RR), odds ratio (OR), and risk difference (RD) were presented. In estimation of the OR and RR, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the RD.
[1] p-value based on the Wald test testing whether the relative risk equals to 1.
[2] p-value from a logistic regression using the penalized likelihood estimation (the FIRTH option) and with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Durch Arzneimittel bedingte Erkrankungen der Leber – Nicht-schwere Ereignisse

Für diesen Endpunkt wurden für die Subgruppenmerkmale Alter, Geschlecht, Abstammung, Region, Vorherige Behandlung mit Tetramer-Stabilisatoren, Genotyp, Kardiale Subpopulation und Gewicht weniger als zehn Ereignisse in den jeweiligen Subgruppenausprägungen berichtet. Daher werden, den Vorgaben des G-BA entsprechend, keine Subgruppenanalysen für diese Subgruppenmerkmale dargestellt.

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Table 11.82
Treatment-Emergent Non-severe Adverse Events Mapped to Drug-related Hepatic Disorders - Comprehensive Search SMQ:
Incidence by System Organ Class and Preferred Term During the 18-Month Treatment Period: Subgroup Analysis
Safety Population

At least 1 AE

Subgroup Statistics	Vutrisiran (HELIOS-A) (N=122) n (%)	Patisiran (HELIOS-A) (N=42) n (%)
Baseline NIS		
<50, n/N1 (%)	5/ 78 (6.4)	5/ 27 (18.5)
Risk difference (Vutrisiran - Patisiran), (95% CI)	-12.108 (-27.736, 3.520)	
Odds ratio (Vutrisiran/Patisiran), (95% CI)	0.301 (0.080, 1.137)	
Relative risk (Vutrisiran/Patisiran), (95% CI)	0.346 (0.109, 1.104)	
P-value [1]	0.0730	
≥50, n/N1 (%)	1/ 44 (2.3)	1/ 15 (6.7)
Risk difference (Vutrisiran - Patisiran), (95% CI)	-4.394 (-17.763, 8.975)	
Odds ratio (Vutrisiran/Patisiran), (95% CI)	0.326 (0.019, 5.554)	
Relative risk (Vutrisiran/Patisiran), (95% CI)	0.341 (0.023, 5.119)	
P-value [1]	0.4362	
P-value of Treatment*Baseline NIS [2]	0.9510	

TEAE = Treatment-emergent adverse event = AE with onset or worsening in severity after first dose through last dose + 84 days (vutrisiran) or + 28 days (patisiran), or AE considered treatment-related at any time after first dose.
Missing severity/relationship imputed to severe/related, respectively.
RR=Relative Risk; OR=Odds Ratio; RD=Risk Difference.
Unstratified RR, OR, and RD were presented.
In estimation of the OR and RR, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the RD.
[1] p-value based on the Wald test testing whether the relative risk equals to 1.
[2] p-value from a logistic regression using the penalized likelihood estimation (the FIRTH option) and with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Table 11.82
Treatment-Emergent Non-severe Adverse Events Mapped to Drug-related Hepatic Disorders - Comprehensive Search SMQ:
Incidence by System Organ Class and Preferred Term During the 18-Month Treatment Period: Subgroup Analysis
Safety Population

At least 1 AE

Subgroup Statistics	Vutrisiran (HELIOS-A) (N=122) n (%)	Patisiran (HELIOS-A) (N=42) n (%)
FAP Stage		
I, n/N1 (%)	5/ 84 (6.0)	5/ 31 (16.1)
Risk difference (Vutrisiran - Patisiran), (95% CI)	-10.177 (-24.077, 3.724)	
Odds ratio (Vutrisiran/Patisiran), (95% CI)	0.329 (0.088, 1.228)	
Relative risk (Vutrisiran/Patisiran), (95% CI)	0.369 (0.115, 1.188)	
P-value [1]	0.0947	
II&III, n/N1 (%)	1/ 38 (2.6)	1/ 11 (9.1)
Risk difference (Vutrisiran - Patisiran), (95% CI)	-6.459 (-24.194, 11.275)	
Odds ratio (Vutrisiran/Patisiran), (95% CI)	0.270 (0.016, 4.712)	
Relative risk (Vutrisiran/Patisiran), (95% CI)	0.289 (0.020, 4.262)	
P-value [1]	0.3663	
P-value of Treatment*FAP Stage [2]	0.9011	

TEAE = Treatment-emergent adverse event = AE with onset or worsening in severity after first dose through last dose + 84 days (vutrisiran) or + 28 days (patisiran), or AE considered treatment-related at any time after first dose.
Missing severity/relationship imputed to severe/related, respectively.
RR=Relative Risk; OR=Odds Ratio; RD=Risk Difference.
Unstratified RR, OR, and RD were presented.
In estimation of the OR and RR, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the RD.
[1] p-value based on the Wald test testing whether the relative risk equals to 1.
[2] p-value from a logistic regression using the penalized likelihood estimation (the FIRTH option) and with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Durch Arzneimittel bedingte Erkrankungen der Leber – Schwere Ereignisse

Für diesen Endpunkt wurden keine Ereignisse auf Ebene der Gesamtpopulation berichtet.

Durch Arzneimittel bedingte Erkrankungen der Leber – Schwerwiegende Ereignisse

Für diesen Endpunkt wurden keine Ereignisse auf Ebene der Gesamtpopulation berichtet.

Herzinsuffizienz

Herzinsuffizienz – Ereignisse jeglichen Schweregrades

Für diesen Endpunkt wurden für die Subgruppenmerkmale Alter, Region, NIS zu Baseline, FAP-Stadium und Kardiale Subpopulation weniger als zehn Ereignisse in den jeweiligen Subgruppenausprägungen berichtet. Daher werden, den Vorgaben des G-BA entsprechend, keine Subgruppenanalysen für diese Subgruppenmerkmale dargestellt.

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Table 11.28
Treatment-Emergent Adverse Events Mapped to Cardiac Failure SMQ (Narrow): Incidence by Preferred Term During the 18-Month Treatment Period: Subgroup Analysis
Safety Population

At least 1 AE

Subgroup Statistics	Vutrisiran (HELIOS-A) (N=122) n (%)	Patisiran (HELIOS-A) (N=42) n (%)
Sex		
Male, n/N1 (%)	6/ 79 (7.6)	5/ 27 (18.5)
Risk difference (Vutrisiran - Patisiran), (95% CI)	-10.924 (-26.697, 4.850)	
Odds ratio (Vutrisiran/Patisiran), (95% CI)	0.362 (0.101, 1.299)	
Relative risk (Vutrisiran/Patisiran), (95% CI)	0.410 (0.136, 1.236)	
P-value [1]	0.1134	
Female, n/N1 (%)	1/ 43 (2.3)	3/ 15 (20.0)
Risk difference (Vutrisiran - Patisiran), (95% CI)	-17.674 (-38.412, 3.063)	
Odds ratio (Vutrisiran/Patisiran), (95% CI)	0.095 (0.009, 1.001)	
Relative risk (Vutrisiran/Patisiran), (95% CI)	0.116 (0.013, 1.034)	
P-value [1]	0.0536	
P-value of Treatment*Sex [2]	0.3894	

TEAE = Treatment-emergent adverse event = AE with onset or worsening in severity after first dose through last dose + 84 days (vutrisiran) or + 28 days (patisiran), or AE considered treatment-related at any time after first dose.
Missing severity/relationship imputed to severe/related, respectively.
Unstratified relative risk (RR), odds ratio (OR), and risk difference (RD) were presented. In estimation of the OR and RR, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the RD.
[1] p-value based on the Wald test testing whether the relative risk equals to 1.
[2] p-value from a logistic regression using the penalized likelihood estimation (the FIRTH option) and with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Table 11.28
Treatment-Emergent Adverse Events Mapped to Cardiac Failure SMQ (Narrow): Incidence by Preferred Term During the 18-Month Treatment Period: Subgroup Analysis
Safety Population

At least 1 AE

Subgroup Statistics	Vutrisiran (HELIOS-A) (N=122) n (%)	Patisiran (HELIOS-A) (N=42) n (%)
Race		
White, n/N1 (%)	6/ 86 (7.0)	6/ 29 (20.7)
Risk difference (Vutrisiran - Patisiran), (95% CI)	-13.713 (-29.408, 1.983)	
Odds ratio (Vutrisiran/Patisiran), (95% CI)	0.288 (0.085, 0.977)	
Relative risk (Vutrisiran/Patisiran), (95% CI)	0.337 (0.118, 0.964)	
P-value [1]	0.0425	
All Other Races, n/N1 (%)	1/ 36 (2.8)	2/ 13 (15.4)
Risk difference (Vutrisiran - Patisiran), (95% CI)	-12.607 (-32.941, 7.728)	
Odds ratio (Vutrisiran/Patisiran), (95% CI)	0.157 (0.013, 1.903)	
Relative risk (Vutrisiran/Patisiran), (95% CI)	0.181 (0.018, 1.828)	
P-value [1]	0.1473	
P-value of Treatment*Race [2]	0.7486	

TEAE = Treatment-emergent adverse event = AE with onset or worsening in severity after first dose through last dose + 84 days (vutrisiran) or + 28 days (patisiran), or AE considered treatment-related at any time after first dose.
Missing severity/relationship imputed to severe/related, respectively.
Unstratified relative risk (RR), odds ratio (OR), and risk difference (RD) were presented. In estimation of the OR and RR, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the RD.
[1] p-value based on the Wald test testing whether the relative risk equals to 1.
[2] p-value from a logistic regression using the penalized likelihood estimation (the FIRTH option) and with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Table 11.28
Treatment-Emergent Adverse Events Mapped to Cardiac Failure SMQ (Narrow): Incidence by Preferred Term During the 18-Month Treatment Period: Subgroup Analysis
Safety Population

At least 1 AE

Subgroup Statistics	Vutrisiran (HELIOS-A) (N=122) n (%)	Patisiran (HELIOS-A) (N=42) n (%)
Previous Tetramer Stabilizer Use		
Yes, n/N1 (%)	4/ 75 (5.3)	6/ 33 (18.2)
Risk difference (Vutrisiran - Patisiran), (95% CI)	-12.848 (-26.956, 1.259)	
Odds ratio (Vutrisiran/Patisiran), (95% CI)	0.254 (0.066, 0.969)	
Relative risk (Vutrisiran/Patisiran), (95% CI)	0.293 (0.089, 0.971)	
P-value [1]	0.0446	
No, n/N1 (%)	3/ 47 (6.4)	2/ 9 (22.2)
Risk difference (Vutrisiran - Patisiran), (95% CI)	-15.839 (-43.885, 12.207)	
Odds ratio (Vutrisiran/Patisiran), (95% CI)	0.239 (0.034, 1.692)	
Relative risk (Vutrisiran/Patisiran), (95% CI)	0.287 (0.056, 1.482)	
P-value [1]	0.1362	
P-value of Treatment*Previous Tetramer Stabilizer Use [2]	0.9169	

TEAE = Treatment-emergent adverse event = AE with onset or worsening in severity after first dose through last dose + 84 days (vutrisiran) or + 28 days (patisiran), or AE considered treatment-related at any time after first dose.
Missing severity/relationship imputed to severe/related, respectively.
Unstratified relative risk (RR), odds ratio (OR), and risk difference (RD) were presented. In estimation of the OR and RR, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the RD.
[1] p-value based on the Wald test testing whether the relative risk equals to 1.
[2] p-value from a logistic regression using the penalized likelihood estimation (the FIRTH option) and with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Table 11.28
Treatment-Emergent Adverse Events Mapped to Cardiac Failure SMQ (Narrow): Incidence by Preferred Term During the 18-Month Treatment Period: Subgroup Analysis
Safety Population

At least 1 AE

Subgroup Statistics	Vutrisiran (HELIOS-A) (N=122) n (%)	Patisiran (HELIOS-A) (N=42) n (%)
Genotype		
V30M, n/N1 (%)	2/ 54 (3.7)	2/ 20 (10.0)
Risk difference (Vutrisiran - Patisiran), (95% CI)	-6.296 (-20.376, 7.783)	
Odds ratio (Vutrisiran/Patisiran), (95% CI)	0.346 (0.045, 2.641)	
Relative risk (Vutrisiran/Patisiran), (95% CI)	0.370 (0.056, 2.456)	
P-value [1]	0.3034	
non-V30M, n/N1 (%)	5/ 68 (7.4)	6/ 22 (27.3)
Risk difference (Vutrisiran - Patisiran), (95% CI)	-19.920 (-39.537, -0.303)	
Odds ratio (Vutrisiran/Patisiran), (95% CI)	0.212 (0.057, 0.782)	
Relative risk (Vutrisiran/Patisiran), (95% CI)	0.270 (0.091, 0.798)	
P-value [1]	0.0179	
P-value of Treatment*Genotype [2]	0.6823	

TEAE = Treatment-emergent adverse event = AE with onset or worsening in severity after first dose through last dose + 84 days (vutrisiran) or + 28 days (patisiran), or AE considered treatment-related at any time after first dose.
Missing severity/relationship imputed to severe/related, respectively.
Unstratified relative risk (RR), odds ratio (OR), and risk difference (RD) were presented. In estimation of the OR and RR, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the RD.
[1] p-value based on the Wald test testing whether the relative risk equals to 1.
[2] p-value from a logistic regression using the penalized likelihood estimation (the FIRTH option) and with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Table 11.28
Treatment-Emergent Adverse Events Mapped to Cardiac Failure SMQ (Narrow): Incidence by Preferred Term During the 18-Month Treatment Period: Subgroup Analysis
Safety Population

At least 1 AE

Subgroup Statistics	Vutrisiran (HELIOS-A) (N=122) n (%)	Patisiran (HELIOS-A) (N=42) n (%)
Weight (kg)		
<65 kg, n/N1 (%)	1/ 46 (2.2)	2/ 15 (13.3)
Risk difference (Vutrisiran - Patisiran), (95% CI)	-11.159 (-28.871, 6.552)	
Odds ratio (Vutrisiran/Patisiran), (95% CI)	0.144 (0.012, 1.722)	
Relative risk (Vutrisiran/Patisiran), (95% CI)	0.163 (0.016, 1.673)	
P-value [1]	0.1269	
>=65 kg, n/N1 (%)	6/ 76 (7.9)	6/ 27 (22.2)
Risk difference (Vutrisiran - Patisiran), (95% CI)	-14.327 (-31.140, 2.485)	
Odds ratio (Vutrisiran/Patisiran), (95% CI)	0.300 (0.087, 1.029)	
Relative risk (Vutrisiran/Patisiran), (95% CI)	0.355 (0.125, 1.008)	
P-value [1]	0.0518	
P-value of Treatment*Weight [2]	0.6692	

TEAE = Treatment-emergent adverse event = AE with onset or worsening in severity after first dose through last dose + 84 days (vutrisiran) or + 28 days (patisiran), or AE considered treatment-related at any time after first dose.
Missing severity/relationship imputed to severe/related, respectively.
Unstratified relative risk (RR), odds ratio (OR), and risk difference (RD) were presented. In estimation of the OR and RR, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the RD.
[1] p-value based on the Wald test testing whether the relative risk equals to 1.
[2] p-value from a logistic regression using the penalized likelihood estimation (the FIRTH option) and with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Herzinsuffizienz – Nicht-schwere Ereignisse

Für diesen Endpunkt wurden insgesamt weniger als zehn Ereignisse auf Ebene der Gesamtpopulation berichtet. Daher werden, den Vorgaben des G-BA entsprechend, keine Subgruppenanalysen für diesen Endpunkt dargestellt.

Herzinsuffizienz – Schwere Ereignisse

Für diesen Endpunkt wurden insgesamt weniger als zehn Ereignisse auf Ebene der Gesamtpopulation berichtet. Daher werden, den Vorgaben des G-BA entsprechend, keine Subgruppenanalysen für diesen Endpunkt dargestellt.

Herzinsuffizienz – Schwerwiegende Ereignisse

Für diesen Endpunkt wurden insgesamt weniger als zehn Ereignisse auf Ebene der Gesamtpopulation berichtet. Daher werden, den Vorgaben des G-BA entsprechend, keine Subgruppenanalysen für diesen Endpunkt dargestellt.

Torsade de Pointes/QT-Verlängerung

Torsade de Pointes/QT-Verlängerung – Ereignisse jeglichen Schweregrades

Für diesen Endpunkt wurden für die Subgruppenmerkmale Geschlecht, Region, NIS zu Baseline, Vorherige Behandlung mit Tetramer-Stabilisatoren, FAP-Stadium und Kardiale Subpopulation weniger als zehn Ereignisse in den jeweiligen Subgruppenausprägungen berichtet. Daher werden, den Vorgaben des G-BA entsprechend, keine Subgruppenanalysen für diese Subgruppenmerkmale dargestellt.

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Table 11.29
Treatment-Emergent Adverse Events Mapped to Torsade de pointes/QT Prolongation SMQ: Incidence by Preferred Term During the 18-Month Treatment Period: Subgroup Analysis
Safety Population

At least 1 AE

Subgroup Statistics	Vutrisiran (HELIOS-A) (N=122) n (%)	Patisiran (HELIOS-A) (N=42) n (%)
Age (years)		
<65, n/N1 (%)	9/ 76 (11.8)	2/ 31 (6.5)
Risk difference (Vutrisiran - Patisiran), (95% CI)	5.390 (-5.904, 16.685)	
Odds ratio (Vutrisiran/Patisiran), (95% CI)	1.948 (0.396, 9.579)	
Relative risk (Vutrisiran/Patisiran), (95% CI)	1.836 (0.420, 8.016)	
P-value [1]	0.4194	
≥65, n/N1 (%)	5/ 46 (10.9)	0/ 11 (0)
Risk difference (Vutrisiran - Patisiran), (95% CI)	10.870 (1.875, 19.864)	
Odds ratio (Vutrisiran/Patisiran), (95% CI)	3.048 (0.157, 59.286)	
Relative risk (Vutrisiran/Patisiran), (95% CI)	2.809 (0.167, 47.345)	
P-value [1]	0.4737	
P-value of Treatment*Age [2]	0.7281	

TEAE = Treatment-emergent adverse event = AE with onset or worsening in severity after first dose through last dose + 84 days (vutrisiran) or + 28 days (patisiran), or AE considered treatment-related at any time after first dose.
Missing severity/relationship imputed to severe/related, respectively.
Unstratified relative risk (RR), odds ratio (OR), and risk difference (RD) were presented. In estimation of the OR and RR, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the RD.
[1] p-value based on the Wald test testing whether the relative risk equals to 1.
[2] p-value from a logistic regression using the penalized likelihood estimation (the FIRTH option) and with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Table 11.29
Treatment-Emergent Adverse Events Mapped to Torsade de pointes/QT Prolongation SMQ: Incidence by Preferred Term During the 18-Month Treatment Period: Subgroup Analysis
Safety Population

At least 1 AE

Subgroup Statistics	Vutrisiran (HELIOS-A) (N=122) n (%)	Patisiran (HELIOS-A) (N=42) n (%)
Race		
White, n/N1 (%)	11/ 86 (12.8)	1/ 29 (3.4)
Risk difference (Vutrisiran - Patisiran), (95% CI)	9.342 (-0.349, 19.034)	
Odds ratio (Vutrisiran/Patisiran), (95% CI)	4.107 (0.507, 33.289)	
Relative risk (Vutrisiran/Patisiran), (95% CI)	3.709 (0.500, 27.501)	
P-value [1]	0.1997	
All Other Races, n/N1 (%)	3/ 36 (8.3)	1/ 13 (7.7)
Risk difference (Vutrisiran - Patisiran), (95% CI)	0.641 (-16.427, 17.709)	
Odds ratio (Vutrisiran/Patisiran), (95% CI)	1.091 (0.103, 11.527)	
Relative risk (Vutrisiran/Patisiran), (95% CI)	1.083 (0.123, 9.512)	
P-value [1]	0.9424	
P-value of Treatment*Race [2]	0.3903	

TEAE = Treatment-emergent adverse event = AE with onset or worsening in severity after first dose through last dose + 84 days (vutrisiran) or + 28 days (patisiran), or AE considered treatment-related at any time after first dose.
Missing severity/relationship imputed to severe/related, respectively.
Unstratified relative risk (RR), odds ratio (OR), and risk difference (RD) were presented. In estimation of the OR and RR, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the RD.
[1] p-value based on the Wald test testing whether the relative risk equals to 1.
[2] p-value from a logistic regression using the penalized likelihood estimation (the FIRTH option) and with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Table 11.29
Treatment-Emergent Adverse Events Mapped to Torsade de pointes/QT Prolongation SMQ: Incidence by Preferred Term During the 18-Month Treatment Period: Subgroup Analysis
Safety Population

At least 1 AE

Subgroup Statistics	Vutrisiran (HELIOS-A) (N=122) n (%)	Patisiran (HELIOS-A) (N=42) n (%)
Genotype		
V30M, n/N1 (%)	4/ 54 (7.4)	1/ 20 (5.0)
Risk difference (Vutrisiran - Patisiran), (95% CI)	2.407 (-9.426, 14.241)	
Odds ratio (Vutrisiran/Patisiran), (95% CI)	1.520 (0.160, 14.480)	
Relative risk (Vutrisiran/Patisiran), (95% CI)	1.481 (0.176, 12.471)	
P-value [1]	0.7177	
non-V30M, n/N1 (%)	10/ 68 (14.7)	1/ 22 (4.5)
Risk difference (Vutrisiran - Patisiran), (95% CI)	10.160 (-1.948, 22.269)	
Odds ratio (Vutrisiran/Patisiran), (95% CI)	3.621 (0.437, 30.025)	
Relative risk (Vutrisiran/Patisiran), (95% CI)	3.235 (0.438, 23.873)	
P-value [1]	0.2496	
P-value of Treatment*Genotype [2]	0.5585	

TEAE = Treatment-emergent adverse event = AE with onset or worsening in severity after first dose through last dose + 84 days (vutrisiran) or + 28 days (patisiran), or AE considered treatment-related at any time after first dose.
Missing severity/relationship imputed to severe/related, respectively.
Unstratified relative risk (RR), odds ratio (OR), and risk difference (RD) were presented. In estimation of the OR and RR, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the RD.
[1] p-value based on the Wald test testing whether the relative risk equals to 1.
[2] p-value from a logistic regression using the penalized likelihood estimation (the FIRTH option) and with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Table 11.29
Treatment-Emergent Adverse Events Mapped to Torsade de pointes/QT Prolongation SMQ: Incidence by Preferred Term During the 18-Month Treatment Period: Subgroup Analysis
Safety Population

At least 1 AE

Subgroup Statistics	Vutrisiran (HELIOS-A) (N=122) n (%)	Patisiran (HELIOS-A) (N=42) n (%)
Weight (kg)		
<65 kg, n/N1 (%)	4/ 46 (8.7)	0/ 15 (0)
Risk difference (Vutrisiran - Patisiran), (95% CI)	8.696 (0.553, 16.838)	
Odds ratio (Vutrisiran/Patisiran), (95% CI)	3.282 (0.167, 64.562)	
Relative risk (Vutrisiran/Patisiran), (95% CI)	3.064 (0.174, 53.829)	
P-value [1]	0.4439	
>=65 kg, n/N1 (%)	10/ 76 (13.2)	2/ 27 (7.4)
Risk difference (Vutrisiran - Patisiran), (95% CI)	5.750 (-6.713, 18.214)	
Odds ratio (Vutrisiran/Patisiran), (95% CI)	1.894 (0.388, 9.254)	
Relative risk (Vutrisiran/Patisiran), (95% CI)	1.776 (0.415, 7.598)	
P-value [1]	0.4384	
P-value of Treatment*Weight [2]	0.6821	

TEAE = Treatment-emergent adverse event = AE with onset or worsening in severity after first dose through last dose + 84 days (vutrisiran) or + 28 days (patisiran), or AE considered treatment-related at any time after first dose.
Missing severity/relationship imputed to severe/related, respectively.
Unstratified relative risk (RR), odds ratio (OR), and risk difference (RD) were presented. In estimation of the OR and RR, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the RD.
[1] p-value based on the Wald test testing whether the relative risk equals to 1.
[2] p-value from a logistic regression using the penalized likelihood estimation (the FIRTH option) and with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Torsade de Pointes/QT-Verlängerung – Nicht-schwere Ereignisse

Für diesen Endpunkt wurden für die Subgruppenmerkmale Geschlecht, Region, NIS zu Baseline, Vorherige Behandlung mit Tetramer-Stabilisatoren, FAP-Stadium und Kardiale Subpopulation weniger als zehn Ereignisse in den jeweiligen Subgruppenausprägungen berichtet. Daher werden, den Vorgaben des G-BA entsprechend, keine Subgruppenanalysen für diese Subgruppenmerkmale dargestellt.

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Table 11.84
Treatment-Emergent Non-severe Adverse Events Mapped to Torsade de pointes/QT Prolongation SMQ: Incidence by Preferred Term During the 18-Month Treatment Period: Subgroup Analysis
Safety Population

At least 1 AE

Subgroup Statistics	Vutrisiran (HELIOS-A) (N=122) n (%)	Patisiran (HELIOS-A) (N=42) n (%)
Age (years)		
<65, n/N1 (%)	9/ 76 (11.8)	2/ 31 (6.5)
Risk difference (Vutrisiran - Patisiran), (95% CI)	5.390 (-5.904, 16.685)	
Odds ratio (Vutrisiran/Patisiran), (95% CI)	1.948 (0.396, 9.579)	
Relative risk (Vutrisiran/Patisiran), (95% CI)	1.836 (0.420, 8.016)	
P-value [1]	0.4194	
≥65, n/N1 (%)	3/ 46 (6.5)	0/ 11 (0)
Risk difference (Vutrisiran - Patisiran), (95% CI)	6.522 (-0.613, 13.657)	
Odds ratio (Vutrisiran/Patisiran), (95% CI)	1.851 (0.089, 38.441)	
Relative risk (Vutrisiran/Patisiran), (95% CI)	1.787 (0.099, 32.306)	
P-value [1]	0.6942	
P-value of Treatment*Age [2]	0.9514	

TEAE = Treatment-emergent adverse event = AE with onset or worsening in severity after first dose through last dose + 84 days (vutrisiran) or + 28 days (patisiran), or AE considered treatment-related at any time after first dose.
Missing severity/relationship imputed to severe/related, respectively.
RR=Relative Risk; OR=Odds Ratio; RD=Risk Difference.
Unstratified RR, OR, and RD were presented.
In estimation of the OR and RR, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the RD.
[1] p-value based on the Wald test testing whether the relative risk equals to 1.
[2] p-value from a logistic regression using the penalized likelihood estimation (the FIRTH option) and with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Table 11.84
Treatment-Emergent Non-severe Adverse Events Mapped to Torsade de pointes/QT Prolongation SMQ: Incidence by Preferred Term During the 18-Month Treatment Period: Subgroup Analysis
Safety Population

At least 1 AE

Subgroup Statistics	Vutrisiran (HELIOS-A) (N=122) n (%)	Patisiran (HELIOS-A) (N=42) n (%)
Race		
White, n/N1 (%)	10/ 86 (11.6)	1/ 29 (3.4)
Risk difference (Vutrisiran - Patisiran), (95% CI)	8.180 (-1.307, 17.667)	
Odds ratio (Vutrisiran/Patisiran), (95% CI)	3.684 (0.451, 30.110)	
Relative risk (Vutrisiran/Patisiran), (95% CI)	3.372 (0.451, 25.219)	
P-value [1]	0.2364	
All Other Races, n/N1 (%)	2/ 36 (5.6)	1/ 13 (7.7)
Risk difference (Vutrisiran - Patisiran), (95% CI)	-2.137 (-18.440, 14.167)	
Odds ratio (Vutrisiran/Patisiran), (95% CI)	0.706 (0.059, 8.506)	
Relative risk (Vutrisiran/Patisiran), (95% CI)	0.722 (0.071, 7.314)	
P-value [1]	0.7829	
P-value of Treatment*Race [2]	0.3104	

TEAE = Treatment-emergent adverse event = AE with onset or worsening in severity after first dose through last dose + 84 days (vutrisiran) or + 28 days (patisiran), or AE considered treatment-related at any time after first dose.
Missing severity/relationship imputed to severe/related, respectively.
RR=Relative Risk; OR=Odds Ratio; RD=Risk Difference.
Unstratified RR, OR, and RD were presented.
In estimation of the OR and RR, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the RD.
[1] p-value based on the Wald test testing whether the relative risk equals to 1.
[2] p-value from a logistic regression using the penalized likelihood estimation (the FIRTH option) and with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Table 11.84
Treatment-Emergent Non-severe Adverse Events Mapped to Torsade de pointes/QT Prolongation SMQ: Incidence by Preferred Term During the 18-Month Treatment Period: Subgroup Analysis
Safety Population

At least 1 AE

Subgroup Statistics	Vutrisiran (HELIOS-A) (N=122) n (%)	Patisiran (HELIOS-A) (N=42) n (%)
Genotype		
V30M, n/N1 (%)	3/ 54 (5.6)	1/ 20 (5.0)
Risk difference (Vutrisiran - Patisiran), (95% CI)	0.556 (-10.783, 11.894)	
Odds ratio (Vutrisiran/Patisiran), (95% CI)	1.118 (0.109, 11.415)	
Relative risk (Vutrisiran/Patisiran), (95% CI)	1.111 (0.123, 10.071)	
P-value [1]	0.9254	
non-V30M, n/N1 (%)	9/ 68 (13.2)	1/ 22 (4.5)
Risk difference (Vutrisiran - Patisiran), (95% CI)	8.690 (-3.169, 20.549)	
Odds ratio (Vutrisiran/Patisiran), (95% CI)	3.203 (0.383, 26.826)	
Relative risk (Vutrisiran/Patisiran), (95% CI)	2.912 (0.390, 21.716)	
P-value [1]	0.2972	
P-value of Treatment*Genotype [2]	0.4937	

TEAE = Treatment-emergent adverse event = AE with onset or worsening in severity after first dose through last dose + 84 days (vutrisiran) or + 28 days (patisiran), or AE considered treatment-related at any time after first dose.
Missing severity/relationship imputed to severe/related, respectively.
RR=Relative Risk; OR=Odds Ratio; RD=Risk Difference.
Unstratified RR, OR, and RD were presented.
In estimation of the OR and RR, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the RD.
[1] p-value based on the Wald test testing whether the relative risk equals to 1.
[2] p-value from a logistic regression using the penalized likelihood estimation (the FIRTH option) and with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Table 11.84
Treatment-Emergent Non-severe Adverse Events Mapped to Torsade de pointes/QT Prolongation SMQ: Incidence by Preferred Term During the 18-Month Treatment Period: Subgroup Analysis
Safety Population

At least 1 AE

Subgroup Statistics	Vutrisiran (HELIOS-A) (N=122) n (%)	Patisiran (HELIOS-A) (N=42) n (%)
Weight (kg)		
<65 kg, n/N1 (%)	4/ 46 (8.7)	0/ 15 (0)
Risk difference (Vutrisiran - Patisiran), (95% CI)	8.696 (0.553, 16.838)	
Odds ratio (Vutrisiran/Patisiran), (95% CI)	3.282 (0.167, 64.562)	
Relative risk (Vutrisiran/Patisiran), (95% CI)	3.064 (0.174, 53.829)	
P-value [1]	0.4439	
>=65 kg, n/N1 (%)	8/ 76 (10.5)	2/ 27 (7.4)
Risk difference (Vutrisiran - Patisiran), (95% CI)	3.119 (-8.931, 15.168)	
Odds ratio (Vutrisiran/Patisiran), (95% CI)	1.471 (0.292, 7.400)	
Relative risk (Vutrisiran/Patisiran), (95% CI)	1.421 (0.322, 6.280)	
P-value [1]	0.6430	
P-value of Treatment*Weight [2]	0.5849	

TEAE = Treatment-emergent adverse event = AE with onset or worsening in severity after first dose through last dose + 84 days (vutrisiran) or + 28 days (patisiran), or AE considered treatment-related at any time after first dose.
Missing severity/relationship imputed to severe/related, respectively.
RR=Relative Risk; OR=Odds Ratio; RD=Risk Difference.
Unstratified RR, OR, and RD were presented.
In estimation of the OR and RR, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the RD.
[1] p-value based on the Wald test testing whether the relative risk equals to 1.
[2] p-value from a logistic regression using the penalized likelihood estimation (the FIRTH option) and with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Torsade de Pointes/QT-Verlängerung – Schwere Ereignisse

Für diesen Endpunkt wurden insgesamt weniger als zehn Ereignisse auf Ebene der Gesamtpopulation berichtet. Daher werden, den Vorgaben des G-BA entsprechend, keine Subgruppenanalysen für diesen Endpunkt dargestellt.

Torsade de Pointes/QT-Verlängerung – Schwerwiegende Ereignisse

Für diesen Endpunkt wurden insgesamt weniger als zehn Ereignisse auf Ebene der Gesamtpopulation berichtet. Daher werden, den Vorgaben des G-BA entsprechend, keine Subgruppenanalysen für diesen Endpunkt dargestellt.

Akutes Nierenversagen

Akutes Nierenversagen – Ereignisse jeglichen Schweregrades

Für diesen Endpunkt wurden insgesamt weniger als zehn Ereignisse auf Ebene der Gesamtpopulation berichtet. Daher werden, den Vorgaben des G-BA entsprechend, keine Subgruppenanalysen für diesen Endpunkt dargestellt.

Akutes Nierenversagen – Nicht-schwere Ereignisse

Für diesen Endpunkt wurden insgesamt weniger als zehn Ereignisse auf Ebene der Gesamtpopulation berichtet. Daher werden, den Vorgaben des G-BA entsprechend, keine Subgruppenanalysen für diesen Endpunkt dargestellt.

Akutes Nierenversagen – Schwere Ereignisse

Für diesen Endpunkt wurden insgesamt weniger als zehn Ereignisse auf Ebene der Gesamtpopulation berichtet. Daher werden, den Vorgaben des G-BA entsprechend, keine Subgruppenanalysen für diesen Endpunkt dargestellt.

Akutes Nierenversagen – Schwerwiegende Ereignisse

Für diesen Endpunkt wurden insgesamt weniger als zehn Ereignisse auf Ebene der Gesamtpopulation berichtet. Daher werden, den Vorgaben des G-BA entsprechend, keine Subgruppenanalysen für diesen Endpunkt dargestellt.

Maligne oder unspezifizierte Tumoren

Maligne oder unspezifizierte Tumoren – Ereignisse jeglichen Schweregrades

Für diesen Endpunkt wurden insgesamt weniger als zehn Ereignisse auf Ebene der Gesamtpopulation berichtet. Daher werden, den Vorgaben des G-BA entsprechend, keine Subgruppenanalysen für diesen Endpunkt dargestellt.

Maligne oder unspezifizierte Tumoren – Nicht-schwere Ereignisse

Für diesen Endpunkt wurden insgesamt weniger als zehn Ereignisse auf Ebene der Gesamtpopulation berichtet. Daher werden, den Vorgaben des G-BA entsprechend, keine Subgruppenanalysen für diesen Endpunkt dargestellt.

Maligne oder unspezifizierte Tumoren – Schwere Ereignisse

Für diesen Endpunkt wurden keine Ereignisse auf Ebene der Gesamtpopulation berichtet.

Maligne oder unspezifizierte Tumoren – Schwerwiegende Ereignisse

Für diesen Endpunkt wurden insgesamt weniger als zehn Ereignisse auf Ebene der Gesamtpopulation berichtet. Daher werden, den Vorgaben des G-BA entsprechend, keine Subgruppenanalysen für diesen Endpunkt dargestellt.

Depression und Suizid/Selbstverletzendes Verhalten

Depression und Suizid/Selbstverletzendes Verhalten – Ereignisse jeglichen Schweregrades

Für diesen Endpunkt wurden insgesamt weniger als zehn Ereignisse auf Ebene der Gesamtpopulation berichtet. Daher werden, den Vorgaben des G-BA entsprechend, keine Subgruppenanalysen für diesen Endpunkt dargestellt.

Depression und Suizid/Selbstverletzendes Verhalten – Nicht-schwere Ereignisse

Für diesen Endpunkt wurden insgesamt weniger als zehn Ereignisse auf Ebene der Gesamtpopulation berichtet. Daher werden, den Vorgaben des G-BA entsprechend, keine Subgruppenanalysen für diesen Endpunkt dargestellt.

Depression und Suizid/Selbstverletzendes Verhalten – Schwere Ereignisse

Für diesen Endpunkt wurden keine Ereignisse auf Ebene der Gesamtpopulation berichtet.

Depression und Suizid/Selbstverletzendes Verhalten – Schwerwiegende Ereignisse

Für diesen Endpunkt wurden keine Ereignisse auf Ebene der Gesamtpopulation berichtet.

Herzrhythmusstörungen

Herzrhythmusstörungen – Ereignisse jeglichen Schweregrades

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Table 11.63
Treatment-Emergent Adverse Events Mapped to Cardiac Arrhythmias (HLGT): Incidence by High Level Term and Preferred Term During the 18-Month Treatment Period: Subgroup Analysis
Safety Population

At least 1 AE

Subgroup Statistics	Vutrisiran (HELIOS-A) (N=122) n (%)	Patisiran (HELIOS-A) (N=42) n (%)
Age (years)		
<65, n/N1 (%)	21/ 76 (27.6)	2/ 31 (6.5)
Risk difference (Vutrisiran - Patisiran), (95% CI)	21.180 (7.919, 34.441)	
Odds ratio (Vutrisiran/Patisiran), (95% CI)	5.536 (1.213, 25.277)	
Relative risk (Vutrisiran/Patisiran), (95% CI)	4.283 (1.068, 17.177)	
P-value [1]	0.0401	
≥65, n/N1 (%)	9/ 46 (19.6)	1/ 11 (9.1)
Risk difference (Vutrisiran - Patisiran), (95% CI)	10.474 (-10.020, 30.969)	
Odds ratio (Vutrisiran/Patisiran), (95% CI)	2.432 (0.275, 21.537)	
Relative risk (Vutrisiran/Patisiran), (95% CI)	2.152 (0.304, 15.255)	
P-value [1]	0.4430	
P-value of Treatment*Age [2]	0.4363	

TEAE = Treatment-emergent adverse event = AE with onset or worsening in severity after first dose through last dose + 84 days (vutrisiran) or + 28 days (patisiran), or AE considered treatment-related at any time after first dose.
Missing severity/relationship imputed to severe/related, respectively.
RR=Relative Risk; OR=Odds Ratio; RD=Risk Difference.
Unstratified RR, OR, and RD were presented.
In estimation of the OR and RR, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the RD.
[1] p-value based on the Wald test testing whether the relative risk equals to 1.
[2] p-value from a logistic regression using the penalized likelihood estimation (the FIRTH option) and with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Table 11.63
Treatment-Emergent Adverse Events Mapped to Cardiac Arrhythmias (HLGT): Incidence by High Level Term and Preferred Term During the 18-Month Treatment Period: Subgroup Analysis
Safety Population

At least 1 AE

Subgroup Statistics	Vutrisiran (HELIOS-A) (N=122) n (%)	Patisiran (HELIOS-A) (N=42) n (%)
Sex		
Male, n/N1 (%)	18/ 79 (22.8)	2/ 27 (7.4)
Risk difference (Vutrisiran - Patisiran), (95% CI)	15.377 (1.845, 28.910)	
Odds ratio (Vutrisiran/Patisiran), (95% CI)	3.689 (0.796, 17.089)	
Relative risk (Vutrisiran/Patisiran), (95% CI)	3.076 (0.763, 12.399)	
P-value [1]	0.1142	
Female, n/N1 (%)	12/ 43 (27.9)	1/ 15 (6.7)
Risk difference (Vutrisiran - Patisiran), (95% CI)	21.240 (2.826, 39.655)	
Odds ratio (Vutrisiran/Patisiran), (95% CI)	5.419 (0.641, 45.850)	
Relative risk (Vutrisiran/Patisiran), (95% CI)	4.186 (0.593, 29.525)	
P-value [1]	0.1509	
P-value of Treatment*Sex [2]	0.8518	

TEAE = Treatment-emergent adverse event = AE with onset or worsening in severity after first dose through last dose + 84 days (vutrisiran) or + 28 days (patisiran), or AE considered treatment-related at any time after first dose.
Missing severity/relationship imputed to severe/related, respectively.
RR=Relative Risk; OR=Odds Ratio; RD=Risk Difference.
Unstratified RR, OR, and RD were presented.
In estimation of the OR and RR, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the RD.
[1] p-value based on the Wald test testing whether the relative risk equals to 1.
[2] p-value from a logistic regression using the penalized likelihood estimation (the FIRTH option) and with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Table 11.63
Treatment-Emergent Adverse Events Mapped to Cardiac Arrhythmias (HLGT): Incidence by High Level Term and Preferred Term During the 18-Month Treatment Period: Subgroup Analysis
Safety Population

At least 1 AE

Subgroup Statistics	Vutrisiran (HELIOS-A) (N=122) n (%)	Patisiran (HELIOS-A) (N=42) n (%)
Race		
White, n/N1 (%)	23/ 86 (26.7)	2/ 29 (6.9)
Risk difference (Vutrisiran - Patisiran), (95% CI)	19.848 (6.711, 32.984)	
Odds ratio (Vutrisiran/Patisiran), (95% CI)	4.929 (1.085, 22.391)	
Relative risk (Vutrisiran/Patisiran), (95% CI)	3.878 (0.973, 15.449)	
P-value [1]	0.0546	
All Other Races, n/N1 (%)	7/ 36 (19.4)	1/ 13 (7.7)
Risk difference (Vutrisiran - Patisiran), (95% CI)	11.752 (-7.663, 31.168)	
Odds ratio (Vutrisiran/Patisiran), (95% CI)	2.897 (0.321, 26.158)	
Relative risk (Vutrisiran/Patisiran), (95% CI)	2.528 (0.343, 18.622)	
P-value [1]	0.3627	
P-value of Treatment*Race [2]	0.5922	

TEAE = Treatment-emergent adverse event = AE with onset or worsening in severity after first dose through last dose + 84 days (vutrisiran) or + 28 days (patisiran), or AE considered treatment-related at any time after first dose.
Missing severity/relationship imputed to severe/related, respectively.
RR=Relative Risk; OR=Odds Ratio; RD=Risk Difference.
Unstratified RR, OR, and RD were presented.
In estimation of the OR and RR, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the RD.
[1] p-value based on the Wald test testing whether the relative risk equals to 1.
[2] p-value from a logistic regression using the penalized likelihood estimation (the FIRTH option) and with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Table 11.63
Treatment-Emergent Adverse Events Mapped to Cardiac Arrhythmias (HLGT): Incidence by High Level Term and Preferred Term During the 18-Month Treatment Period: Subgroup Analysis
Safety Population

At least 1 AE

Subgroup Statistics	Vutrisiran (HELIOS-A) (N=122) n (%)	Patisiran (HELIOS-A) (N=42) n (%)
Region		
North America, n/N1 (%)	4/ 27 (14.8)	0/ 8 (0)
Risk difference (Vutrisiran - Patisiran), (95% CI)	14.815 (1.415, 28.215)	
Odds ratio (Vutrisiran/Patisiran), (95% CI)	3.255 (0.158, 67.055)	
Relative risk (Vutrisiran/Patisiran), (95% CI)	2.893 (0.172, 48.707)	
P-value [1]	0.4609	
Western Europe, n/N1 (%)	6/ 42 (14.3)	2/ 20 (10.0)
Risk difference (Vutrisiran - Patisiran), (95% CI)	4.286 (-12.592, 21.164)	
Odds ratio (Vutrisiran/Patisiran), (95% CI)	1.500 (0.275, 8.189)	
Relative risk (Vutrisiran/Patisiran), (95% CI)	1.429 (0.316, 6.461)	
P-value [1]	0.6432	

TEAE = Treatment-emergent adverse event = AE with onset or worsening in severity after first dose through last dose + 84 days (vutrisiran) or + 28 days (patisiran), or AE considered treatment-related at any time after first dose.
Missing severity/relationship imputed to severe/related, respectively.
RR=Relative Risk; OR=Odds Ratio; RD=Risk Difference.
Unstratified RR, OR, and RD were presented.
In estimation of the OR and RR, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the RD.
[1] p-value based on the Wald test testing whether the relative risk equals to 1.
[2] p-value from a logistic regression using the penalized likelihood estimation (the FIRTH option) and with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Table 11.63
Treatment-Emergent Adverse Events Mapped to Cardiac Arrhythmias (HLGT): Incidence by High Level Term and Preferred Term During the 18-Month Treatment Period: Subgroup Analysis
Safety Population

At least 1 AE

Subgroup Statistics	Vutrisiran (HELIOS-A) (N=122) n (%)	Patisiran (HELIOS-A) (N=42) n (%)
Rest of World, n/N1 (%)	20/ 53 (37.7)	1/ 14 (7.1)
Risk difference (Vutrisiran - Patisiran), (95% CI)	30.593 (11.824, 49.362)	
Odds ratio (Vutrisiran/Patisiran), (95% CI)	7.879 (0.957, 64.884)	
Relative risk (Vutrisiran/Patisiran), (95% CI)	5.283 (0.774, 36.038)	
P-value [1]	0.0893	
P-value of Treatment*Region [2]	0.5069	

TEAE = Treatment-emergent adverse event = AE with onset or worsening in severity after first dose through last dose + 84 days (vutrisiran) or + 28 days (patisiran), or AE considered treatment-related at any time after first dose.
Missing severity/relationship imputed to severe/related, respectively.
RR=Relative Risk; OR=Odds Ratio; RD=Risk Difference.
Unstratified RR, OR, and RD were presented.
In estimation of the OR and RR, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the RD.
[1] p-value based on the Wald test testing whether the relative risk equals to 1.
[2] p-value from a logistic regression using the penalized likelihood estimation (the FIRTH option) and with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Table 11.63
Treatment-Emergent Adverse Events Mapped to Cardiac Arrhythmias (HLGT): Incidence by High Level Term and Preferred Term During the 18-Month Treatment Period: Subgroup Analysis
Safety Population

At least 1 AE

Subgroup Statistics	Vutrisiran (HELIOS-A) (N=122) n (%)	Patisiran (HELIOS-A) (N=42) n (%)
Baseline NIS		
<50, n/N1 (%)	20/ 78 (25.6)	2/ 27 (7.4)
Risk difference (Vutrisiran - Patisiran), (95% CI)	18.234 (4.396, 32.071)	
Odds ratio (Vutrisiran/Patisiran), (95% CI)	4.310 (0.936, 19.853)	
Relative risk (Vutrisiran/Patisiran), (95% CI)	3.462 (0.866, 13.843)	
P-value [1]	0.0791	
≥50, n/N1 (%)	10/ 44 (22.7)	1/ 15 (6.7)
Risk difference (Vutrisiran - Patisiran), (95% CI)	16.061 (-1.622, 33.743)	
Odds ratio (Vutrisiran/Patisiran), (95% CI)	4.118 (0.481, 35.271)	
Relative risk (Vutrisiran/Patisiran), (95% CI)	3.409 (0.475, 24.454)	
P-value [1]	0.2225	
P-value of Treatment*Baseline NIS [2]	0.8707	

TEAE = Treatment-emergent adverse event = AE with onset or worsening in severity after first dose through last dose + 84 days (vutrisiran) or + 28 days (patisiran), or AE considered treatment-related at any time after first dose.
Missing severity/relationship imputed to severe/related, respectively.
RR=Relative Risk; OR=Odds Ratio; RD=Risk Difference.
Unstratified RR, OR, and RD were presented.
In estimation of the OR and RR, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the RD.
[1] p-value based on the Wald test testing whether the relative risk equals to 1.
[2] p-value from a logistic regression using the penalized likelihood estimation (the FIRTH option) and with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Table 11.63
Treatment-Emergent Adverse Events Mapped to Cardiac Arrhythmias (HLGT): Incidence by High Level Term and Preferred Term During the 18-Month Treatment Period: Subgroup Analysis
Safety Population

At least 1 AE

Subgroup Statistics	Vutrisiran (HELIOS-A) (N=122) n (%)	Patisiran (HELIOS-A) (N=42) n (%)
Previous Tetramer Stabilizer Use		
Yes, n/N1 (%)	17/ 75 (22.7)	2/ 33 (6.1)
Risk difference (Vutrisiran - Patisiran), (95% CI)	16.606 (4.114, 29.098)	
Odds ratio (Vutrisiran/Patisiran), (95% CI)	4.543 (0.985, 20.953)	
Relative risk (Vutrisiran/Patisiran), (95% CI)	3.740 (0.916, 15.270)	
P-value [1]	0.0661	
No, n/N1 (%)	13/ 47 (27.7)	1/ 9 (11.1)
Risk difference (Vutrisiran - Patisiran), (95% CI)	16.548 (-7.640, 40.737)	
Odds ratio (Vutrisiran/Patisiran), (95% CI)	3.059 (0.348, 26.921)	
Relative risk (Vutrisiran/Patisiran), (95% CI)	2.489 (0.371, 16.724)	
P-value [1]	0.3480	
P-value of Treatment*Previous Tetramer Stabilizer Use [2]	0.6642	

TEAE = Treatment-emergent adverse event = AE with onset or worsening in severity after first dose through last dose + 84 days (vutrisiran) or + 28 days (patisiran), or AE considered treatment-related at any time after first dose.
Missing severity/relationship imputed to severe/related, respectively.
RR=Relative Risk; OR=Odds Ratio; RD=Risk Difference.
Unstratified RR, OR, and RD were presented.
In estimation of the OR and RR, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the RD.
[1] p-value based on the Wald test testing whether the relative risk equals to 1.
[2] p-value from a logistic regression using the penalized likelihood estimation (the FIRTH option) and with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Table 11.63
Treatment-Emergent Adverse Events Mapped to Cardiac Arrhythmias (HLGT): Incidence by High Level Term and Preferred Term During the 18-Month Treatment Period: Subgroup Analysis
Safety Population

At least 1 AE

Subgroup Statistics	Vutrisiran (HELIOS-A) (N=122) n (%)	Patisiran (HELIOS-A) (N=42) n (%)
Genotype		
V30M, n/N1 (%)	10/ 54 (18.5)	1/ 20 (5.0)
Risk difference (Vutrisiran - Patisiran), (95% CI)	13.519 (-0.573, 27.610)	
Odds ratio (Vutrisiran/Patisiran), (95% CI)	4.318 (0.516, 36.151)	
Relative risk (Vutrisiran/Patisiran), (95% CI)	3.704 (0.506, 27.110)	
P-value [1]	0.1973	
non-V30M, n/N1 (%)	20/ 68 (29.4)	2/ 22 (9.1)
Risk difference (Vutrisiran - Patisiran), (95% CI)	20.321 (4.147, 36.495)	
Odds ratio (Vutrisiran/Patisiran), (95% CI)	4.167 (0.889, 19.520)	
Relative risk (Vutrisiran/Patisiran), (95% CI)	3.235 (0.821, 12.754)	
P-value [1]	0.0934	
P-value of Treatment*Genotype [2]	0.9181	

TEAE = Treatment-emergent adverse event = AE with onset or worsening in severity after first dose through last dose + 84 days (vutrisiran) or + 28 days (patisiran), or AE considered treatment-related at any time after first dose.
Missing severity/relationship imputed to severe/related, respectively.
RR=Relative Risk; OR=Odds Ratio; RD=Risk Difference.
Unstratified RR, OR, and RD were presented.
In estimation of the OR and RR, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the RD.
[1] p-value based on the Wald test testing whether the relative risk equals to 1.
[2] p-value from a logistic regression using the penalized likelihood estimation (the FIRTH option) and with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Table 11.63
Treatment-Emergent Adverse Events Mapped to Cardiac Arrhythmias (HLGT): Incidence by High Level Term and Preferred Term During the 18-Month Treatment Period: Subgroup Analysis
Safety Population

At least 1 AE

Subgroup Statistics	Vutrisiran (HELIOS-A) (N=122) n (%)	Patisiran (HELIOS-A) (N=42) n (%)
FAP Stage		
I, n/N1 (%)	20/ 84 (23.8)	3/ 31 (9.7)
Risk difference (Vutrisiran - Patisiran), (95% CI)	14.132 (0.302, 27.962)	
Odds ratio (Vutrisiran/Patisiran), (95% CI)	2.917 (0.801, 10.619)	
Relative risk (Vutrisiran/Patisiran), (95% CI)	2.460 (0.786, 7.704)	
P-value [1]	0.1221	
II&III, n/N1 (%)	10/ 38 (26.3)	0/ 11 (0)
Risk difference (Vutrisiran - Patisiran), (95% CI)	26.316 (12.315, 40.317)	
Odds ratio (Vutrisiran/Patisiran), (95% CI)	8.474 (0.458, 156.876)	
Relative risk (Vutrisiran/Patisiran), (95% CI)	6.462 (0.408, 102.324)	
P-value [1]	0.1855	
P-value of Treatment*FAP Stage [2]	0.4790	

TEAE = Treatment-emergent adverse event = AE with onset or worsening in severity after first dose through last dose + 84 days (vutrisiran) or + 28 days (patisiran), or AE considered treatment-related at any time after first dose.
Missing severity/relationship imputed to severe/related, respectively.
RR=Relative Risk; OR=Odds Ratio; RD=Risk Difference.
Unstratified RR, OR, and RD were presented.
In estimation of the OR and RR, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the RD.
[1] p-value based on the Wald test testing whether the relative risk equals to 1.
[2] p-value from a logistic regression using the penalized likelihood estimation (the FIRTH option) and with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Table 11.63
Treatment-Emergent Adverse Events Mapped to Cardiac Arrhythmias (HLGT): Incidence by High Level Term and Preferred Term During the 18-Month Treatment Period: Subgroup Analysis
Safety Population

At least 1 AE

Subgroup Statistics	Vutrisiran (HELIOS-A) (N=122) n (%)	Patisiran (HELIOS-A) (N=42) n (%)
Cardiac Subpopulation		
Yes, n/N1 (%)	13/ 40 (32.5)	1/ 14 (7.1)
Risk difference (Vutrisiran - Patisiran), (95% CI)	25.357 (5.541, 45.173)	
Odds ratio (Vutrisiran/Patisiran), (95% CI)	6.259 (0.737, 53.140)	
Relative risk (Vutrisiran/Patisiran), (95% CI)	4.550 (0.653, 31.686)	
P-value [1]	0.1260	
No, n/N1 (%)	17/ 82 (20.7)	2/ 28 (7.1)
Risk difference (Vutrisiran - Patisiran), (95% CI)	13.589 (0.628, 26.550)	
Odds ratio (Vutrisiran/Patisiran), (95% CI)	3.400 (0.733, 15.767)	
Relative risk (Vutrisiran/Patisiran), (95% CI)	2.902 (0.715, 11.781)	
P-value [1]	0.1360	
P-value of Treatment*Cardiac Subpopulation [2]	0.7107	

TEAE = Treatment-emergent adverse event = AE with onset or worsening in severity after first dose through last dose + 84 days (vutrisiran) or + 28 days (patisiran), or AE considered treatment-related at any time after first dose.
Missing severity/relationship imputed to severe/related, respectively.
RR=Relative Risk; OR=Odds Ratio; RD=Risk Difference.
Unstratified RR, OR, and RD were presented.
In estimation of the OR and RR, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the RD.
[1] p-value based on the Wald test testing whether the relative risk equals to 1.
[2] p-value from a logistic regression using the penalized likelihood estimation (the FIRTH option) and with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Table 11.63
Treatment-Emergent Adverse Events Mapped to Cardiac Arrhythmias (HLGT): Incidence by High Level Term and Preferred Term During the 18-Month Treatment Period: Subgroup Analysis
Safety Population

At least 1 AE

Subgroup Statistics	Vutrisiran (HELIOS-A) (N=122) n (%)	Patisiran (HELIOS-A) (N=42) n (%)
Weight (kg)		
<65 kg, n/N1 (%)	10/ 46 (21.7)	1/ 15 (6.7)
Risk difference (Vutrisiran - Patisiran), (95% CI)	15.072 (-2.289, 32.434)	
Odds ratio (Vutrisiran/Patisiran), (95% CI)	3.889 (0.455, 33.263)	
Relative risk (Vutrisiran/Patisiran), (95% CI)	3.261 (0.454, 23.413)	
P-value [1]	0.2399	
>=65 kg, n/N1 (%)	20/ 76 (26.3)	2/ 27 (7.4)
Risk difference (Vutrisiran - Patisiran), (95% CI)	18.908 (4.923, 32.894)	
Odds ratio (Vutrisiran/Patisiran), (95% CI)	4.464 (0.969, 20.578)	
Relative risk (Vutrisiran/Patisiran), (95% CI)	3.553 (0.889, 14.201)	
P-value [1]	0.0730	
P-value of Treatment*Weight [2]	0.8111	

TEAE = Treatment-emergent adverse event = AE with onset or worsening in severity after first dose through last dose + 84 days (vutrisiran) or + 28 days (patisiran), or AE considered treatment-related at any time after first dose.
Missing severity/relationship imputed to severe/related, respectively.
RR=Relative Risk; OR=Odds Ratio; RD=Risk Difference.
Unstratified RR, OR, and RD were presented.
In estimation of the OR and RR, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the RD.
[1] p-value based on the Wald test testing whether the relative risk equals to 1.
[2] p-value from a logistic regression using the penalized likelihood estimation (the FIRTH option) and with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Herzrhythmusstörungen – Nicht-schwere Ereignisse

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Table 11.90
Treatment-Emergent Non-Severe Adverse Events Mapped to Cardiac Arrhythmias (HLGT): Incidence by High Level Term and Preferred Term During the 18-Month Treatment Period: Subgroup Analysis
Safety Population

At least 1 AE

Subgroup Statistics	Vutrisiran (HELIOS-A) (N=122) n (%)	Patisiran (HELIOS-A) (N=42) n (%)
Age (years)		
<65, n/N1 (%)	20/ 76 (26.3)	2/ 31 (6.5)
Risk difference (Vutrisiran - Patisiran), (95% CI)	19.864 (6.719, 33.010)	
Odds ratio (Vutrisiran/Patisiran), (95% CI)	5.179 (1.131, 23.705)	
Relative risk (Vutrisiran/Patisiran), (95% CI)	4.079 (1.014, 16.413)	
P-value [1]	0.0478	
≥65, n/N1 (%)	8/ 46 (17.4)	0/ 11 (0)
Risk difference (Vutrisiran - Patisiran), (95% CI)	17.391 (6.438, 28.345)	
Odds ratio (Vutrisiran/Patisiran), (95% CI)	5.078 (0.272, 94.834)	
Relative risk (Vutrisiran/Patisiran), (95% CI)	4.340 (0.269, 70.021)	
P-value [1]	0.3008	
P-value of Treatment*Age [2]	0.9209	

TEAE = Treatment-emergent adverse event = AE with onset or worsening in severity after first dose through last dose + 84 days (vutrisiran) or + 28 days (patisiran), or AE considered treatment-related at any time after first dose.
Missing severity/relationship imputed to severe/related, respectively.
RR=Relative Risk; OR=Odds Ratio; RD=Risk Difference.
Unstratified RR, OR, and RD were presented.
In estimation of the OR and RR, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the RD.
[1] p-value based on the Wald test testing whether the relative risk equals to 1.
[2] p-value from a logistic regression using the penalized likelihood estimation (the FIRTH option) and with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Table 11.90
Treatment-Emergent Non-Severe Adverse Events Mapped to Cardiac Arrhythmias (HLGT): Incidence by High Level Term and Preferred Term During the 18-Month Treatment Period: Subgroup Analysis
Safety Population

At least 1 AE

Subgroup Statistics	Vutrisiran (HELIOS-A) (N=122) n (%)	Patisiran (HELIOS-A) (N=42) n (%)
Sex		
Male, n/N1 (%)	17/ 79 (21.5)	1/ 27 (3.7)
Risk difference (Vutrisiran - Patisiran), (95% CI)	17.815 (6.289, 29.342)	
Odds ratio (Vutrisiran/Patisiran), (95% CI)	7.129 (0.901, 56.390)	
Relative risk (Vutrisiran/Patisiran), (95% CI)	5.810 (0.811, 41.616)	
P-value [1]	0.0798	
Female, n/N1 (%)	11/ 43 (25.6)	1/ 15 (6.7)
Risk difference (Vutrisiran - Patisiran), (95% CI)	18.915 (0.765, 37.065)	
Odds ratio (Vutrisiran/Patisiran), (95% CI)	4.813 (0.565, 40.956)	
Relative risk (Vutrisiran/Patisiran), (95% CI)	3.837 (0.540, 27.267)	
P-value [1]	0.1789	
P-value of Treatment*Sex [2]	0.7777	

TEAE = Treatment-emergent adverse event = AE with onset or worsening in severity after first dose through last dose + 84 days (vutrisiran) or + 28 days (patisiran), or AE considered treatment-related at any time after first dose.
Missing severity/relationship imputed to severe/related, respectively.
RR=Relative Risk; OR=Odds Ratio; RD=Risk Difference.
Unstratified RR, OR, and RD were presented.
In estimation of the OR and RR, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the RD.
[1] p-value based on the Wald test testing whether the relative risk equals to 1.
[2] p-value from a logistic regression using the penalized likelihood estimation (the FIRTH option) and with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Table 11.90
Treatment-Emergent Non-Severe Adverse Events Mapped to Cardiac Arrhythmias (HLGT): Incidence by High Level Term and Preferred Term During the 18-Month Treatment Period: Subgroup Analysis
Safety Population

At least 1 AE

Subgroup Statistics	Vutrisiran (HELIOS-A) (N=122) n (%)	Patisiran (HELIOS-A) (N=42) n (%)
Race		
White, n/N1 (%)	21/ 86 (24.4)	1/ 29 (3.4)
Risk difference (Vutrisiran - Patisiran), (95% CI)	20.970 (9.721, 32.219)	
Odds ratio (Vutrisiran/Patisiran), (95% CI)	9.046 (1.159, 70.582)	
Relative risk (Vutrisiran/Patisiran), (95% CI)	7.081 (0.996, 50.346)	
P-value [1]	0.0505	
All Other Races, n/N1 (%)	7/ 36 (19.4)	1/ 13 (7.7)
Risk difference (Vutrisiran - Patisiran), (95% CI)	11.752 (-7.663, 31.168)	
Odds ratio (Vutrisiran/Patisiran), (95% CI)	2.897 (0.321, 26.158)	
Relative risk (Vutrisiran/Patisiran), (95% CI)	2.528 (0.343, 18.622)	
P-value [1]	0.3627	
P-value of Treatment*Race [2]	0.4163	

TEAE = Treatment-emergent adverse event = AE with onset or worsening in severity after first dose through last dose + 84 days (vutrisiran) or + 28 days (patisiran), or AE considered treatment-related at any time after first dose.
Missing severity/relationship imputed to severe/related, respectively.
RR=Relative Risk; OR=Odds Ratio; RD=Risk Difference.
Unstratified RR, OR, and RD were presented.
In estimation of the OR and RR, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the RD.
[1] p-value based on the Wald test testing whether the relative risk equals to 1.
[2] p-value from a logistic regression using the penalized likelihood estimation (the FIRTH option) and with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Table 11.90
Treatment-Emergent Non-Severe Adverse Events Mapped to Cardiac Arrhythmias (HLGT): Incidence by High Level Term and Preferred Term During the 18-Month Treatment Period: Subgroup Analysis
Safety Population

At least 1 AE

Subgroup Statistics	Vutrisiran (HELIOS-A) (N=122) n (%)	Patisiran (HELIOS-A) (N=42) n (%)
Region		
North America, n/N1 (%)	4/ 27 (14.8)	0/ 8 (0)
Risk difference (Vutrisiran - Patisiran), (95% CI)	14.815 (1.415, 28.215)	
Odds ratio (Vutrisiran/Patisiran), (95% CI)	3.255 (0.158, 67.055)	
Relative risk (Vutrisiran/Patisiran), (95% CI)	2.893 (0.172, 48.707)	
P-value [1]	0.4609	
Western Europe, n/N1 (%)	5/ 42 (11.9)	1/ 20 (5.0)
Risk difference (Vutrisiran - Patisiran), (95% CI)	6.905 (-6.776, 20.585)	
Odds ratio (Vutrisiran/Patisiran), (95% CI)	2.568 (0.280, 23.573)	
Relative risk (Vutrisiran/Patisiran), (95% CI)	2.381 (0.297, 19.057)	
P-value [1]	0.4137	

TEAE = Treatment-emergent adverse event = AE with onset or worsening in severity after first dose through last dose + 84 days (vutrisiran) or + 28 days (patisiran), or AE considered treatment-related at any time after first dose.
Missing severity/relationship imputed to severe/related, respectively.
RR=Relative Risk; OR=Odds Ratio; RD=Risk Difference.
Unstratified RR, OR, and RD were presented.
In estimation of the OR and RR, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the RD.
[1] p-value based on the Wald test testing whether the relative risk equals to 1.
[2] p-value from a logistic regression using the penalized likelihood estimation (the FIRTH option) and with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Table 11.90
Treatment-Emergent Non-Severe Adverse Events Mapped to Cardiac Arrhythmias (HLGT): Incidence by High Level Term and Preferred Term During the 18-Month Treatment Period: Subgroup Analysis
Safety Population

At least 1 AE

Subgroup Statistics	Vutrisiran (HELIOS-A) (N=122) n (%)	Patisiran (HELIOS-A) (N=42) n (%)
Rest of World, n/N1 (%)	19/ 53 (35.8)	1/ 14 (7.1)
Risk difference (Vutrisiran - Patisiran), (95% CI)	28.706 (10.033, 47.379)	
Odds ratio (Vutrisiran/Patisiran), (95% CI)	7.265 (0.881, 59.921)	
Relative risk (Vutrisiran/Patisiran), (95% CI)	5.019 (0.734, 34.326)	
P-value [1]	0.1001	
P-value of Treatment*Region [2]	0.7700	

TEAE = Treatment-emergent adverse event = AE with onset or worsening in severity after first dose through last dose + 84 days (vutrisiran) or + 28 days (patisiran), or AE considered treatment-related at any time after first dose.
Missing severity/relationship imputed to severe/related, respectively.
RR=Relative Risk; OR=Odds Ratio; RD=Risk Difference.
Unstratified RR, OR, and RD were presented.
In estimation of the OR and RR, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the RD.
[1] p-value based on the Wald test testing whether the relative risk equals to 1.
[2] p-value from a logistic regression using the penalized likelihood estimation (the FIRTH option) and with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Table 11.90
Treatment-Emergent Non-Severe Adverse Events Mapped to Cardiac Arrhythmias (HLGT): Incidence by High Level Term and Preferred Term During the 18-Month Treatment Period: Subgroup Analysis
Safety Population

At least 1 AE

Subgroup Statistics	Vutrisiran (HELIOS-A) (N=122) n (%)	Patisiran (HELIOS-A) (N=42) n (%)
Baseline NIS		
<50, n/N1 (%)	19/ 78 (24.4)	2/ 27 (7.4)
Risk difference (Vutrisiran - Patisiran), (95% CI)	16.952 (3.228, 30.675)	
Odds ratio (Vutrisiran/Patisiran), (95% CI)	4.025 (0.871, 18.595)	
Relative risk (Vutrisiran/Patisiran), (95% CI)	3.288 (0.819, 13.199)	
P-value [1]	0.0932	
≥50, n/N1 (%)	9/ 44 (20.5)	0/ 15 (0)
Risk difference (Vutrisiran - Patisiran), (95% CI)	20.455 (8.536, 32.373)	
Odds ratio (Vutrisiran/Patisiran), (95% CI)	8.296 (0.454, 151.637)	
Relative risk (Vutrisiran/Patisiran), (95% CI)	6.756 (0.417, 109.549)	
P-value [1]	0.1790	
P-value of Treatment*Baseline NIS [2]	0.5910	

TEAE = Treatment-emergent adverse event = AE with onset or worsening in severity after first dose through last dose + 84 days (vutrisiran) or + 28 days (patisiran), or AE considered treatment-related at any time after first dose.
Missing severity/relationship imputed to severe/related, respectively.
RR=Relative Risk; OR=Odds Ratio; RD=Risk Difference.
Unstratified RR, OR, and RD were presented.
In estimation of the OR and RR, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the RD.
[1] p-value based on the Wald test testing whether the relative risk equals to 1.
[2] p-value from a logistic regression using the penalized likelihood estimation (the FIRTH option) and with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Table 11.90
Treatment-Emergent Non-Severe Adverse Events Mapped to Cardiac Arrhythmias (HLGT): Incidence by High Level Term and Preferred Term During the 18-Month Treatment Period: Subgroup Analysis
Safety Population

At least 1 AE

Subgroup Statistics	Vutrisiran (HELIOS-A) (N=122) n (%)	Patisiran (HELIOS-A) (N=42) n (%)
Previous Tetramer Stabilizer Use		
Yes, n/N1 (%)	16/ 75 (21.3)	2/ 33 (6.1)
Risk difference (Vutrisiran - Patisiran), (95% CI)	15.273 (2.934, 27.611)	
Odds ratio (Vutrisiran/Patisiran), (95% CI)	4.203 (0.908, 19.469)	
Relative risk (Vutrisiran/Patisiran), (95% CI)	3.520 (0.858, 14.444)	
P-value [1]	0.0806	
No, n/N1 (%)	12/ 47 (25.5)	0/ 9 (0)
Risk difference (Vutrisiran - Patisiran), (95% CI)	25.532 (13.066, 37.998)	
Odds ratio (Vutrisiran/Patisiran), (95% CI)	6.690 (0.362, 123.543)	
Relative risk (Vutrisiran/Patisiran), (95% CI)	5.208 (0.335, 80.933)	
P-value [1]	0.2384	
P-value of Treatment*Previous Tetramer Stabilizer Use [2]	0.7065	

TEAE = Treatment-emergent adverse event = AE with onset or worsening in severity after first dose through last dose + 84 days (vutrisiran) or + 28 days (patisiran), or AE considered treatment-related at any time after first dose.
Missing severity/relationship imputed to severe/related, respectively.
RR=Relative Risk; OR=Odds Ratio; RD=Risk Difference.
Unstratified RR, OR, and RD were presented.
In estimation of the OR and RR, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the RD.
[1] p-value based on the Wald test testing whether the relative risk equals to 1.
[2] p-value from a logistic regression using the penalized likelihood estimation (the FIRTH option) and with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Table 11.90
Treatment-Emergent Non-Severe Adverse Events Mapped to Cardiac Arrhythmias (HLGT): Incidence by High Level Term and Preferred Term During the 18-Month Treatment Period: Subgroup Analysis
Safety Population

At least 1 AE

Subgroup Statistics	Vutrisiran (HELIOS-A) (N=122) n (%)	Patisiran (HELIOS-A) (N=42) n (%)
Genotype		
V30M, n/N1 (%)	9/ 54 (16.7)	1/ 20 (5.0)
Risk difference (Vutrisiran - Patisiran), (95% CI)	11.667 (-2.119, 25.452)	
Odds ratio (Vutrisiran/Patisiran), (95% CI)	3.800 (0.450, 32.119)	
Relative risk (Vutrisiran/Patisiran), (95% CI)	3.333 (0.451, 24.661)	
P-value [1]	0.2383	
non-V30M, n/N1 (%)	19/ 68 (27.9)	1/ 22 (4.5)
Risk difference (Vutrisiran - Patisiran), (95% CI)	23.396 (9.630, 37.162)	
Odds ratio (Vutrisiran/Patisiran), (95% CI)	8.143 (1.023, 64.844)	
Relative risk (Vutrisiran/Patisiran), (95% CI)	6.147 (0.872, 43.317)	
P-value [1]	0.0683	
P-value of Treatment*Genotype [2]	0.5744	

TEAE = Treatment-emergent adverse event = AE with onset or worsening in severity after first dose through last dose + 84 days (vutrisiran) or + 28 days (patisiran), or AE considered treatment-related at any time after first dose.
Missing severity/relationship imputed to severe/related, respectively.
RR=Relative Risk; OR=Odds Ratio; RD=Risk Difference.
Unstratified RR, OR, and RD were presented.
In estimation of the OR and RR, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the RD.
[1] p-value based on the Wald test testing whether the relative risk equals to 1.
[2] p-value from a logistic regression using the penalized likelihood estimation (the FIRTH option) and with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Table 11.90
Treatment-Emergent Non-Severe Adverse Events Mapped to Cardiac Arrhythmias (HLGT): Incidence by High Level Term and Preferred Term During the 18-Month Treatment Period: Subgroup Analysis
Safety Population

At least 1 AE

Subgroup Statistics	Vutrisiran (HELIOS-A) (N=122) n (%)	Patisiran (HELIOS-A) (N=42) n (%)
FAP Stage		
I, n/N1 (%)	19/ 84 (22.6)	2/ 31 (6.5)
Risk difference (Vutrisiran - Patisiran), (95% CI)	16.167 (3.724, 28.611)	
Odds ratio (Vutrisiran/Patisiran), (95% CI)	4.238 (0.926, 19.405)	
Relative risk (Vutrisiran/Patisiran), (95% CI)	3.506 (0.867, 14.183)	
P-value [1]	0.0785	
II&III, n/N1 (%)	9/ 38 (23.7)	0/ 11 (0)
Risk difference (Vutrisiran - Patisiran), (95% CI)	23.684 (10.167, 37.202)	
Odds ratio (Vutrisiran/Patisiran), (95% CI)	7.407 (0.398, 137.923)	
Relative risk (Vutrisiran/Patisiran), (95% CI)	5.846 (0.367, 93.225)	
P-value [1]	0.2114	
P-value of Treatment*FAP Stage [2]	0.6634	

TEAE = Treatment-emergent adverse event = AE with onset or worsening in severity after first dose through last dose + 84 days (vutrisiran) or + 28 days (patisiran), or AE considered treatment-related at any time after first dose.
Missing severity/relationship imputed to severe/related, respectively.
RR=Relative Risk; OR=Odds Ratio; RD=Risk Difference.
Unstratified RR, OR, and RD were presented.
In estimation of the OR and RR, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the RD.
[1] p-value based on the Wald test testing whether the relative risk equals to 1.
[2] p-value from a logistic regression using the penalized likelihood estimation (the FIRTH option) and with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Table 11.90
Treatment-Emergent Non-Severe Adverse Events Mapped to Cardiac Arrhythmias (HLGT): Incidence by High Level Term and Preferred Term During the 18-Month Treatment Period: Subgroup Analysis
Safety Population

At least 1 AE

Subgroup Statistics	Vutrisiran (HELIOS-A) (N=122) n (%)	Patisiran (HELIOS-A) (N=42) n (%)
Cardiac Subpopulation		
Yes, n/N1 (%)	11/ 40 (27.5)	1/ 14 (7.1)
Risk difference (Vutrisiran - Patisiran), (95% CI)	20.357 (1.032, 39.682)	
Odds ratio (Vutrisiran/Patisiran), (95% CI)	4.931 (0.575, 42.294)	
Relative risk (Vutrisiran/Patisiran), (95% CI)	3.850 (0.545, 27.184)	
P-value [1]	0.1764	
No, n/N1 (%)	17/ 82 (20.7)	1/ 28 (3.6)
Risk difference (Vutrisiran - Patisiran), (95% CI)	17.160 (6.014, 28.306)	
Odds ratio (Vutrisiran/Patisiran), (95% CI)	7.062 (0.895, 55.744)	
Relative risk (Vutrisiran/Patisiran), (95% CI)	5.805 (0.809, 41.651)	
P-value [1]	0.0803	
P-value of Treatment*Cardiac Subpopulation [2]	0.7992	

TEAE = Treatment-emergent adverse event = AE with onset or worsening in severity after first dose through last dose + 84 days (vutrisiran) or + 28 days (patisiran), or AE considered treatment-related at any time after first dose.
Missing severity/relationship imputed to severe/related, respectively.
RR=Relative Risk; OR=Odds Ratio; RD=Risk Difference.
Unstratified RR, OR, and RD were presented.
In estimation of the OR and RR, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the RD.
[1] p-value based on the Wald test testing whether the relative risk equals to 1.
[2] p-value from a logistic regression using the penalized likelihood estimation (the FIRTH option) and with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Table 11.90
Treatment-Emergent Non-Severe Adverse Events Mapped to Cardiac Arrhythmias (HLGT): Incidence by High Level Term and Preferred Term During the 18-Month Treatment Period: Subgroup Analysis
Safety Population

At least 1 AE

Subgroup Statistics	Vutrisiran (HELIOS-A) (N=122) n (%)	Patisiran (HELIOS-A) (N=42) n (%)
Weight (kg)		
<65 kg, n/N1 (%)	10/ 46 (21.7)	1/ 15 (6.7)
Risk difference (Vutrisiran - Patisiran), (95% CI)	15.072 (-2.289, 32.434)	
Odds ratio (Vutrisiran/Patisiran), (95% CI)	3.889 (0.455, 33.263)	
Relative risk (Vutrisiran/Patisiran), (95% CI)	3.261 (0.454, 23.413)	
P-value [1]	0.2399	
>=65 kg, n/N1 (%)	18/ 76 (23.7)	1/ 27 (3.7)
Risk difference (Vutrisiran - Patisiran), (95% CI)	19.981 (8.060, 31.901)	
Odds ratio (Vutrisiran/Patisiran), (95% CI)	8.069 (1.022, 63.698)	
Relative risk (Vutrisiran/Patisiran), (95% CI)	6.395 (0.896, 45.635)	
P-value [1]	0.0642	
P-value of Treatment*Weight [2]	0.5939	

TEAE = Treatment-emergent adverse event = AE with onset or worsening in severity after first dose through last dose + 84 days (vutrisiran) or + 28 days (patisiran), or AE considered treatment-related at any time after first dose.
Missing severity/relationship imputed to severe/related, respectively.
RR=Relative Risk; OR=Odds Ratio; RD=Risk Difference.
Unstratified RR, OR, and RD were presented.
In estimation of the OR and RR, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the RD.
[1] p-value based on the Wald test testing whether the relative risk equals to 1.
[2] p-value from a logistic regression using the penalized likelihood estimation (the FIRTH option) and with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Herzrhythmusstörungen – Schwere Ereignisse

Für diesen Endpunkt wurden insgesamt weniger als zehn Ereignisse auf Ebene der Gesamtpopulation berichtet. Daher werden, den Vorgaben des G-BA entsprechend, keine Subgruppenanalysen für diesen Endpunkt dargestellt.

Herzrhythmusstörungen – Schwerwiegende Ereignisse

Für diesen Endpunkt wurden insgesamt weniger als zehn Ereignisse auf Ebene der Gesamtpopulation berichtet. Daher werden, den Vorgaben des G-BA entsprechend, keine Subgruppenanalysen für diesen Endpunkt dargestellt.

UE im Zusammenhang mit COVID-19

UE im Zusammenhang mit COVID-19 – Ereignisse jeglichen Schweregrades

Für diesen Endpunkt wurden für kein Subgruppenmerkmal zehn oder mehr Ereignisse in den jeweiligen Subgruppenausprägungen berichtet. Daher werden, den Vorgaben des G-BA entsprechend, keine Subgruppenanalysen für diesen Endpunkt dargestellt.

UE im Zusammenhang mit COVID-19 – Nicht-schwere Ereignisse

Für diesen Endpunkt wurden insgesamt weniger als zehn Ereignisse auf Ebene der Gesamtpopulation berichtet. Daher werden, den Vorgaben des G-BA entsprechend, keine Subgruppenanalysen für diesen Endpunkt dargestellt.

UE im Zusammenhang mit COVID-19 – Schwere Ereignisse

Für diesen Endpunkt wurden insgesamt weniger als zehn Ereignisse auf Ebene der Gesamtpopulation berichtet. Daher werden, den Vorgaben des G-BA entsprechend, keine Subgruppenanalysen für diesen Endpunkt dargestellt.

UE im Zusammenhang mit COVID-19 – Schwerwiegende Ereignisse

Für diesen Endpunkt wurden insgesamt weniger als zehn Ereignisse auf Ebene der Gesamtpopulation berichtet. Daher werden, den Vorgaben des G-BA entsprechend, keine Subgruppenanalysen für diesen Endpunkt dargestellt.

UE im Zusammenhang mit der Gabe von Kortikosteroiden/Prämedikationen

UE im Zusammenhang mit der Gabe von Kortikosteroiden/Prämedikationen – Ereignisse jeglichen Schweregrades

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Table 11.34
Treatment-Emergent Adverse Events Associated with Corticosteroid/Premedication Use: Incidence by System Organ Class and Preferred Term
During the 18-Month Treatment Period: Subgroup Analysis
Safety Population

At least 1 AE

Subgroup Statistics	Vutrisiran (HELIOS-A) (N=122) n (%)	Patisiran (HELIOS-A) (N=42) n (%)
Age (years)		
<65, n/N1 (%)	17/ 76 (22.4)	17/ 31 (54.8)
Risk difference (Vutrisiran - Patisiran), (95% CI)	-32.470 (-52.336, -12.604)	
Odds ratio (Vutrisiran/Patisiran), (95% CI)	0.237 (0.097, 0.578)	
Relative risk (Vutrisiran/Patisiran), (95% CI)	0.408 (0.241, 0.691)	
P-value [1]	0.0008	
≥65, n/N1 (%)	10/ 46 (21.7)	2/ 11 (18.2)
Risk difference (Vutrisiran - Patisiran), (95% CI)	3.557 (-22.164, 29.279)	
Odds ratio (Vutrisiran/Patisiran), (95% CI)	1.250 (0.232, 6.739)	
Relative risk (Vutrisiran/Patisiran), (95% CI)	1.196 (0.304, 4.697)	
P-value [1]	0.7980	
P-value of Treatment*Age [2]	0.1099	

TEAE = Treatment-emergent adverse event = AE with onset or worsening in severity after first dose through last dose + 84 days (vutrisiran) or + 28 days (patisiran), or AE considered treatment-related at any time after first dose.
Events were defined as those associated with premedications in CSR Table 14.3.1.19. For the Patisiran group, TEAEs of the same SOC and PT but not deemed as associated with premedications were also included in this table.
Unstratified relative risk (RR), odds ratio (OR), and risk difference (RD) were presented. In estimation of the OR and RR, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the RD.
[1] p-value based on the Wald test testing whether the relative risk equals to 1.
[2] p-value from a logistic regression using the penalized likelihood estimation (the FIRTH option) and with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Table 11.34
Treatment-Emergent Adverse Events Associated with Corticosteroid/Premedication Use: Incidence by System Organ Class and Preferred Term
During the 18-Month Treatment Period: Subgroup Analysis
Safety Population

At least 1 AE

Subgroup Statistics	Vutrisiran (HELIOS-A) (N=122) n (%)	Patisiran (HELIOS-A) (N=42) n (%)
Sex		
Male, n/N1 (%)	11/ 79 (13.9)	11/ 27 (40.7)
Risk difference (Vutrisiran - Patisiran), (95% CI)	-26.817 (-46.861, -6.772)	
Odds ratio (Vutrisiran/Patisiran), (95% CI)	0.235 (0.087, 0.638)	
Relative risk (Vutrisiran/Patisiran), (95% CI)	0.342 (0.168, 0.697)	
P-value [1]	0.0031	
Female, n/N1 (%)	16/ 43 (37.2)	8/ 15 (53.3)
Risk difference (Vutrisiran - Patisiran), (95% CI)	-16.124 (-45.212, 12.964)	
Odds ratio (Vutrisiran/Patisiran), (95% CI)	0.519 (0.158, 1.701)	
Relative risk (Vutrisiran/Patisiran), (95% CI)	0.698 (0.378, 1.287)	
P-value [1]	0.2491	
P-value of Treatment*Sex [2]	0.3183	

TEAE = Treatment-emergent adverse event = AE with onset or worsening in severity after first dose through last dose + 84 days (vutrisiran) or + 28 days (patisiran), or AE considered treatment-related at any time after first dose.
Events were defined as those associated with premedications in CSR Table 14.3.1.19. For the Patisiran group, TEAEs of the same SOC and PT but not deemed as associated with premedications were also included in this table.
Unstratified relative risk (RR), odds ratio (OR), and risk difference (RD) were presented. In estimation of the OR and RR, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the RD.
[1] p-value based on the Wald test testing whether the relative risk equals to 1.
[2] p-value from a logistic regression using the penalized likelihood estimation (the FIRTH option) and with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Table 11.34
Treatment-Emergent Adverse Events Associated with Corticosteroid/Premedication Use: Incidence by System Organ Class and Preferred Term
During the 18-Month Treatment Period: Subgroup Analysis
Safety Population

At least 1 AE

Subgroup Statistics	Vutrisiran (HELIOS-A) (N=122) n (%)	Patisiran (HELIOS-A) (N=42) n (%)
Race		
White, n/N1 (%)	19/ 86 (22.1)	15/ 29 (51.7)
Risk difference (Vutrisiran - Patisiran), (95% CI)	-29.631 (-49.821, -9.441)	
Odds ratio (Vutrisiran/Patisiran), (95% CI)	0.265 (0.109, 0.644)	
Relative risk (Vutrisiran/Patisiran), (95% CI)	0.427 (0.251, 0.726)	
P-value [1]	0.0017	
All Other Races, n/N1 (%)	8/ 36 (22.2)	4/ 13 (30.8)
Risk difference (Vutrisiran - Patisiran), (95% CI)	-8.547 (-37.076, 19.982)	
Odds ratio (Vutrisiran/Patisiran), (95% CI)	0.643 (0.156, 2.649)	
Relative risk (Vutrisiran/Patisiran), (95% CI)	0.722 (0.261, 2.001)	
P-value [1]	0.5314	
P-value of Treatment*Race [2]	0.3170	

TEAE = Treatment-emergent adverse event = AE with onset or worsening in severity after first dose through last dose + 84 days (vutrisiran) or + 28 days (patisiran), or AE considered treatment-related at any time after first dose.
Events were defined as those associated with premedications in CSR Table 14.3.1.19. For the Patisiran group, TEAEs of the same SOC and PT but not deemed as associated with premedications were also included in this table.
Unstratified relative risk (RR), odds ratio (OR), and risk difference (RD) were presented. In estimation of the OR and RR, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the RD.
[1] p-value based on the Wald test testing whether the relative risk equals to 1.
[2] p-value from a logistic regression using the penalized likelihood estimation (the FIRTH option) and with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Table 11.34
Treatment-Emergent Adverse Events Associated with Corticosteroid/Premedication Use: Incidence by System Organ Class and Preferred Term
During the 18-Month Treatment Period: Subgroup Analysis
Safety Population

At least 1 AE

Subgroup Statistics	Vutrisiran (HELIOS-A) (N=122) n (%)	Patisiran (HELIOS-A) (N=42) n (%)
Region		
North America, n/N1 (%)	9/ 27 (33.3)	5/ 8 (62.5)
Risk difference (Vutrisiran - Patisiran), (95% CI)	-29.167 (-67.135, 8.802)	
Odds ratio (Vutrisiran/Patisiran), (95% CI)	0.300 (0.058, 1.546)	
Relative risk (Vutrisiran/Patisiran), (95% CI)	0.533 (0.250, 1.137)	
P-value [1]	0.1035	
Western Europe, n/N1 (%)	9/ 42 (21.4)	9/ 20 (45.0)
Risk difference (Vutrisiran - Patisiran), (95% CI)	-23.571 (-48.659, 1.516)	
Odds ratio (Vutrisiran/Patisiran), (95% CI)	0.333 (0.106, 1.051)	
Relative risk (Vutrisiran/Patisiran), (95% CI)	0.476 (0.224, 1.013)	
P-value [1]	0.0541	

TEAE = Treatment-emergent adverse event = AE with onset or worsening in severity after first dose through last dose + 84 days (vutrisiran) or + 28 days (patisiran), or AE considered treatment-related at any time after first dose.
Events were defined as those associated with premedications in CSR Table 14.3.1.19. For the Patisiran group, TEAEs of the same SOC and PT but not deemed as associated with premedications were also included in this table.
Unstratified relative risk (RR), odds ratio (OR), and risk difference (RD) were presented. In estimation of the OR and RR, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the RD.
[1] p-value based on the Wald test testing whether the relative risk equals to 1.
[2] p-value from a logistic regression using the penalized likelihood estimation (the FIRTH option) and with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Table 11.34
Treatment-Emergent Adverse Events Associated with Corticosteroid/Premedication Use: Incidence by System Organ Class and Preferred Term
During the 18-Month Treatment Period: Subgroup Analysis
Safety Population

At least 1 AE

Subgroup Statistics	Vutrisiran (HELIOS-A) (N=122) n (%)	Patisiran (HELIOS-A) (N=42) n (%)
Rest of World, n/N1 (%)	9/ 53 (17.0)	5/ 14 (35.7)
Risk difference (Vutrisiran - Patisiran), (95% CI)	-18.733 (-45.792, 8.325)	
Odds ratio (Vutrisiran/Patisiran), (95% CI)	0.368 (0.100, 1.361)	
Relative risk (Vutrisiran/Patisiran), (95% CI)	0.475 (0.189, 1.194)	
P-value [1]	0.1136	
P-value of Treatment*Region [2]	0.9930	

TEAE = Treatment-emergent adverse event = AE with onset or worsening in severity after first dose through last dose + 84 days (vutrisiran) or + 28 days (patisiran), or AE considered treatment-related at any time after first dose.
Events were defined as those associated with premedications in CSR Table 14.3.1.19. For the Patisiran group, TEAEs of the same SOC and PT but not deemed as associated with premedications were also included in this table.
Unstratified relative risk (RR), odds ratio (OR), and risk difference (RD) were presented. In estimation of the OR and RR, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the RD.
[1] p-value based on the Wald test testing whether the relative risk equals to 1.
[2] p-value from a logistic regression using the penalized likelihood estimation (the FIRTH option) and with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Table 11.34
Treatment-Emergent Adverse Events Associated with Corticosteroid/Premedication Use: Incidence by System Organ Class and Preferred Term
During the 18-Month Treatment Period: Subgroup Analysis
Safety Population

At least 1 AE

Subgroup Statistics	Vutrisiran (HELIOS-A) (N=122) n (%)	Patisiran (HELIOS-A) (N=42) n (%)
Baseline NIS		
<50, n/N1 (%)	18/ 78 (23.1)	18/ 27 (66.7)
Risk difference (Vutrisiran - Patisiran), (95% CI)	-43.590 (-63.679, -23.500)	
Odds ratio (Vutrisiran/Patisiran), (95% CI)	0.150 (0.058, 0.391)	
Relative risk (Vutrisiran/Patisiran), (95% CI)	0.346 (0.213, 0.562)	
P-value [1]	<0.0001	
≥50, n/N1 (%)	9/ 44 (20.5)	1/ 15 (6.7)
Risk difference (Vutrisiran - Patisiran), (95% CI)	13.788 (-3.573, 31.149)	
Odds ratio (Vutrisiran/Patisiran), (95% CI)	3.600 (0.416, 31.121)	
Relative risk (Vutrisiran/Patisiran), (95% CI)	3.068 (0.423, 22.247)	
P-value [1]	0.2674	
P-value of Treatment*Baseline NIS [2]	0.0092	

TEAE = Treatment-emergent adverse event = AE with onset or worsening in severity after first dose through last dose + 84 days (vutrisiran) or + 28 days (patisiran), or AE considered treatment-related at any time after first dose.
Events were defined as those associated with premedications in CSR Table 14.3.1.19. For the Patisiran group, TEAEs of the same SOC and PT but not deemed as associated with premedications were also included in this table.
Unstratified relative risk (RR), odds ratio (OR), and risk difference (RD) were presented. In estimation of the OR and RR, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the RD.
[1] p-value based on the Wald test testing whether the relative risk equals to 1.
[2] p-value from a logistic regression using the penalized likelihood estimation (the FIRTH option) and with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Table 11.34
Treatment-Emergent Adverse Events Associated with Corticosteroid/Premedication Use: Incidence by System Organ Class and Preferred Term
During the 18-Month Treatment Period: Subgroup Analysis
Safety Population

At least 1 AE

Subgroup Statistics	Vutrisiran (HELIOS-A) (N=122) n (%)	Patisiran (HELIOS-A) (N=42) n (%)
Previous Tetramer Stabilizer Use		
Yes, n/N1 (%)	12/ 75 (16.0)	14/ 33 (42.4)
Risk difference (Vutrisiran - Patisiran), (95% CI)	-26.424 (-45.217, -7.631)	
Odds ratio (Vutrisiran/Patisiran), (95% CI)	0.259 (0.102, 0.653)	
Relative risk (Vutrisiran/Patisiran), (95% CI)	0.377 (0.196, 0.725)	
P-value [1]	0.0034	
No, n/N1 (%)	15/ 47 (31.9)	5/ 9 (55.6)
Risk difference (Vutrisiran - Patisiran), (95% CI)	-23.641 (-58.733, 11.452)	
Odds ratio (Vutrisiran/Patisiran), (95% CI)	0.375 (0.088, 1.600)	
Relative risk (Vutrisiran/Patisiran), (95% CI)	0.574 (0.280, 1.178)	
P-value [1]	0.1304	
P-value of Treatment*Previous Tetramer Stabilizer Use [2]	0.6579	

TEAE = Treatment-emergent adverse event = AE with onset or worsening in severity after first dose through last dose + 84 days (vutrisiran) or + 28 days (patisiran), or AE considered treatment-related at any time after first dose.
Events were defined as those associated with premedications in CSR Table 14.3.1.19. For the Patisiran group, TEAEs of the same SOC and PT but not deemed as associated with premedications were also included in this table.
Unstratified relative risk (RR), odds ratio (OR), and risk difference (RD) were presented. In estimation of the OR and RR, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the RD.
[1] p-value based on the Wald test testing whether the relative risk equals to 1.
[2] p-value from a logistic regression using the penalized likelihood estimation (the FIRTH option) and with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Table 11.34
Treatment-Emergent Adverse Events Associated with Corticosteroid/Premedication Use: Incidence by System Organ Class and Preferred Term
During the 18-Month Treatment Period: Subgroup Analysis
Safety Population

At least 1 AE

Subgroup Statistics	Vutrisiran (HELIOS-A) (N=122) n (%)	Patisiran (HELIOS-A) (N=42) n (%)
Genotype		
V30M, n/N1 (%)	11/ 54 (20.4)	11/ 20 (55.0)
Risk difference (Vutrisiran - Patisiran), (95% CI)	-34.630 (-58.935, -10.324)	
Odds ratio (Vutrisiran/Patisiran), (95% CI)	0.209 (0.070, 0.630)	
Relative risk (Vutrisiran/Patisiran), (95% CI)	0.370 (0.191, 0.716)	
P-value [1]	0.0032	
non-V30M, n/N1 (%)	16/ 68 (23.5)	8/ 22 (36.4)
Risk difference (Vutrisiran - Patisiran), (95% CI)	-12.834 (-35.322, 9.654)	
Odds ratio (Vutrisiran/Patisiran), (95% CI)	0.538 (0.192, 1.514)	
Relative risk (Vutrisiran/Patisiran), (95% CI)	0.647 (0.322, 1.302)	
P-value [1]	0.2225	
P-value of Treatment*Genotype [2]	0.2422	

TEAE = Treatment-emergent adverse event = AE with onset or worsening in severity after first dose through last dose + 84 days (vutrisiran) or + 28 days (patisiran), or AE considered treatment-related at any time after first dose.
Events were defined as those associated with premedications in CSR Table 14.3.1.19. For the Patisiran group, TEAEs of the same SOC and PT but not deemed as associated with premedications were also included in this table.
Unstratified relative risk (RR), odds ratio (OR), and risk difference (RD) were presented. In estimation of the OR and RR, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the RD.
[1] p-value based on the Wald test testing whether the relative risk equals to 1.
[2] p-value from a logistic regression using the penalized likelihood estimation (the FIRTH option) and with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Table 11.34
Treatment-Emergent Adverse Events Associated with Corticosteroid/Premedication Use: Incidence by System Organ Class and Preferred Term
During the 18-Month Treatment Period: Subgroup Analysis
Safety Population

At least 1 AE

Subgroup Statistics	Vutrisiran (HELIOS-A) (N=122) n (%)	Patisiran (HELIOS-A) (N=42) n (%)
FAP Stage		
I, n/N1 (%)	19/ 84 (22.6)	18/ 31 (58.1)
Risk difference (Vutrisiran - Patisiran), (95% CI)	-35.445 (-54.985, -15.906)	
Odds ratio (Vutrisiran/Patisiran), (95% CI)	0.211 (0.088, 0.508)	
Relative risk (Vutrisiran/Patisiran), (95% CI)	0.390 (0.237, 0.640)	
P-value [1]	0.0002	
II&III, n/N1 (%)	8/ 38 (21.1)	1/ 11 (9.1)
Risk difference (Vutrisiran - Patisiran), (95% CI)	11.962 (-9.407, 33.331)	
Odds ratio (Vutrisiran/Patisiran), (95% CI)	2.667 (0.296, 24.033)	
Relative risk (Vutrisiran/Patisiran), (95% CI)	2.316 (0.324, 16.565)	
P-value [1]	0.4029	
P-value of Treatment*FAP Stage [2]	0.0438	

TEAE = Treatment-emergent adverse event = AE with onset or worsening in severity after first dose through last dose + 84 days (vutrisiran) or + 28 days (patisiran), or AE considered treatment-related at any time after first dose.
Events were defined as those associated with premedications in CSR Table 14.3.1.19. For the Patisiran group, TEAEs of the same SOC and PT but not deemed as associated with premedications were also included in this table.
Unstratified relative risk (RR), odds ratio (OR), and risk difference (RD) were presented. In estimation of the OR and RR, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the RD.
[1] p-value based on the Wald test testing whether the relative risk equals to 1.
[2] p-value from a logistic regression using the penalized likelihood estimation (the FIRTH option) and with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Table 11.34
Treatment-Emergent Adverse Events Associated with Corticosteroid/Premedication Use: Incidence by System Organ Class and Preferred Term
During the 18-Month Treatment Period: Subgroup Analysis
Safety Population

At least 1 AE

Subgroup Statistics	Vutrisiran (HELIOS-A) (N=122) n (%)	Patisiran (HELIOS-A) (N=42) n (%)
Cardiac Subpopulation		
Yes, n/N1 (%)	9/ 40 (22.5)	2/ 14 (14.3)
Risk difference (Vutrisiran - Patisiran), (95% CI)	8.214 (-14.223, 30.652)	
Odds ratio (Vutrisiran/Patisiran), (95% CI)	1.742 (0.328, 9.261)	
Relative risk (Vutrisiran/Patisiran), (95% CI)	1.575 (0.386, 6.426)	
P-value [1]	0.5266	
No, n/N1 (%)	18/ 82 (22.0)	17/ 28 (60.7)
Risk difference (Vutrisiran - Patisiran), (95% CI)	-38.763 (-58.950, -18.576)	
Odds ratio (Vutrisiran/Patisiran), (95% CI)	0.182 (0.072, 0.457)	
Relative risk (Vutrisiran/Patisiran), (95% CI)	0.362 (0.218, 0.599)	
P-value [1]	<0.0001	
P-value of Treatment*Cardiac Subpopulation [2]	0.0262	

TEAE = Treatment-emergent adverse event = AE with onset or worsening in severity after first dose through last dose + 84 days (vutrisiran) or + 28 days (patisiran), or AE considered treatment-related at any time after first dose.
Events were defined as those associated with premedications in CSR Table 14.3.1.19. For the Patisiran group, TEAEs of the same SOC and PT but not deemed as associated with premedications were also included in this table.
Unstratified relative risk (RR), odds ratio (OR), and risk difference (RD) were presented. In estimation of the OR and RR, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the RD.
[1] p-value based on the Wald test testing whether the relative risk equals to 1.
[2] p-value from a logistic regression using the penalized likelihood estimation (the FIRTH option) and with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Table 11.34
Treatment-Emergent Adverse Events Associated with Corticosteroid/Premedication Use: Incidence by System Organ Class and Preferred Term
During the 18-Month Treatment Period: Subgroup Analysis
Safety Population

At least 1 AE

Subgroup Statistics	Vutrisiran (HELIOS-A) (N=122) n (%)	Patisiran (HELIOS-A) (N=42) n (%)
Weight (kg)		
<65 kg, n/N1 (%)	9/ 46 (19.6)	10/ 15 (66.7)
Risk difference (Vutrisiran - Patisiran), (95% CI)	-47.101 (-73.569, -20.634)	
Odds ratio (Vutrisiran/Patisiran), (95% CI)	0.122 (0.033, 0.445)	
Relative risk (Vutrisiran/Patisiran), (95% CI)	0.293 (0.148, 0.583)	
P-value [1]	0.0005	
>=65 kg, n/N1 (%)	18/ 76 (23.7)	9/ 27 (33.3)
Risk difference (Vutrisiran - Patisiran), (95% CI)	-9.649 (-29.836, 10.538)	
Odds ratio (Vutrisiran/Patisiran), (95% CI)	0.621 (0.238, 1.620)	
Relative risk (Vutrisiran/Patisiran), (95% CI)	0.711 (0.364, 1.387)	
P-value [1]	0.3166	
P-value of Treatment*Weight [2]	0.0603	

TEAE = Treatment-emergent adverse event = AE with onset or worsening in severity after first dose through last dose + 84 days (vutrisiran) or + 28 days (patisiran), or AE considered treatment-related at any time after first dose.
Events were defined as those associated with premedications in CSR Table 14.3.1.19. For the Patisiran group, TEAEs of the same SOC and PT but not deemed as associated with premedications were also included in this table.
Unstratified relative risk (RR), odds ratio (OR), and risk difference (RD) were presented. In estimation of the OR and RR, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the RD.
[1] p-value based on the Wald test testing whether the relative risk equals to 1.
[2] p-value from a logistic regression using the penalized likelihood estimation (the FIRTH option) and with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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UE im Zusammenhang mit der Gabe von Kortikosteroiden/Prämedikationen – Nicht-schwere Ereignisse

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Table 11.89
Treatment-Emergent Non-severe Adverse Events Associated with Corticosteroid/Premedication Use: Incidence by System Organ Class and Preferred Term
During the 18-Month Treatment Period: Subgroup Analysis
Safety Population

At least 1 AE

Subgroup Statistics	Vutrisiran (HELIOS-A) (N=122) n (%)	Patisiran (HELIOS-A) (N=42) n (%)
Age (years)		
<65, n/N1 (%)	17/ 76 (22.4)	17/ 31 (54.8)
Risk difference (Vutrisiran - Patisiran), (95% CI)	-32.470 (-52.336, -12.604)	
Odds ratio (Vutrisiran/Patisiran), (95% CI)	0.237 (0.097, 0.578)	
Relative risk (Vutrisiran/Patisiran), (95% CI)	0.408 (0.241, 0.691)	
P-value [1]	0.0008	
≥65, n/N1 (%)	10/ 46 (21.7)	2/ 11 (18.2)
Risk difference (Vutrisiran - Patisiran), (95% CI)	3.557 (-22.164, 29.279)	
Odds ratio (Vutrisiran/Patisiran), (95% CI)	1.250 (0.232, 6.739)	
Relative risk (Vutrisiran/Patisiran), (95% CI)	1.196 (0.304, 4.697)	
P-value [1]	0.7980	
P-value of Treatment*Age [2]	0.1099	

TEAE = Treatment-emergent adverse event = AE with onset or worsening in severity after first dose through last dose + 84 days (vutrisiran) or + 28 days (patisiran), or AE considered treatment-related at any time after first dose.
Events were defined as those associated with premedications in CSR Table 14.3.1.19. For the Patisiran group, TEAEs of the same SOC and PT but not deemed as associated with premedications were also included in this table.
RR=Relative Risk; OR=Odds Ratio; RD=Risk Difference.
Unstratified RR, OR, and RD were presented.
In estimation of the OR and RR, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the RD.
[1] p-value based on the Wald test testing whether the relative risk equals to 1.
[2] p-value from a logistic regression using the penalized likelihood estimation (the FIRTH option) and with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Table 11.89
Treatment-Emergent Non-severe Adverse Events Associated with Corticosteroid/Premedication Use: Incidence by System Organ Class and Preferred Term
During the 18-Month Treatment Period: Subgroup Analysis
Safety Population

At least 1 AE

Subgroup Statistics	Vutrisiran (HELIOS-A) (N=122) n (%)	Patisiran (HELIOS-A) (N=42) n (%)
Sex		
Male, n/N1 (%)	11/ 79 (13.9)	11/ 27 (40.7)
Risk difference (Vutrisiran - Patisiran), (95% CI)	-26.817 (-46.861, -6.772)	
Odds ratio (Vutrisiran/Patisiran), (95% CI)	0.235 (0.087, 0.638)	
Relative risk (Vutrisiran/Patisiran), (95% CI)	0.342 (0.168, 0.697)	
P-value [1]	0.0031	
Female, n/N1 (%)	16/ 43 (37.2)	8/ 15 (53.3)
Risk difference (Vutrisiran - Patisiran), (95% CI)	-16.124 (-45.212, 12.964)	
Odds ratio (Vutrisiran/Patisiran), (95% CI)	0.519 (0.158, 1.701)	
Relative risk (Vutrisiran/Patisiran), (95% CI)	0.698 (0.378, 1.287)	
P-value [1]	0.2491	
P-value of Treatment*Sex [2]	0.3183	

TEAE = Treatment-emergent adverse event = AE with onset or worsening in severity after first dose through last dose + 84 days (vutrisiran) or + 28 days (patisiran), or AE considered treatment-related at any time after first dose.
Events were defined as those associated with premedications in CSR Table 14.3.1.19. For the Patisiran group, TEAEs of the same SOC and PT but not deemed as associated with premedications were also included in this table.
RR=Relative Risk; OR=Odds Ratio; RD=Risk Difference.
Unstratified RR, OR, and RD were presented.
In estimation of the OR and RR, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the RD.
[1] p-value based on the Wald test testing whether the relative risk equals to 1.
[2] p-value from a logistic regression using the penalized likelihood estimation (the FIRTH option) and with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Table 11.89
Treatment-Emergent Non-severe Adverse Events Associated with Corticosteroid/Premedication Use: Incidence by System Organ Class and Preferred Term
During the 18-Month Treatment Period: Subgroup Analysis
Safety Population

At least 1 AE

Subgroup Statistics	Vutrisiran (HELIOS-A) (N=122) n (%)	Patisiran (HELIOS-A) (N=42) n (%)
Race		
White, n/N1 (%)	19/ 86 (22.1)	15/ 29 (51.7)
Risk difference (Vutrisiran - Patisiran), (95% CI)	-29.631 (-49.821, -9.441)	
Odds ratio (Vutrisiran/Patisiran), (95% CI)	0.265 (0.109, 0.644)	
Relative risk (Vutrisiran/Patisiran), (95% CI)	0.427 (0.251, 0.726)	
P-value [1]	0.0017	
All Other Races, n/N1 (%)	8/ 36 (22.2)	4/ 13 (30.8)
Risk difference (Vutrisiran - Patisiran), (95% CI)	-8.547 (-37.076, 19.982)	
Odds ratio (Vutrisiran/Patisiran), (95% CI)	0.643 (0.156, 2.649)	
Relative risk (Vutrisiran/Patisiran), (95% CI)	0.722 (0.261, 2.001)	
P-value [1]	0.5314	
P-value of Treatment*Race [2]	0.3170	

TEAE = Treatment-emergent adverse event = AE with onset or worsening in severity after first dose through last dose + 84 days (vutrisiran) or + 28 days (patisiran), or AE considered treatment-related at any time after first dose.
Events were defined as those associated with premedications in CSR Table 14.3.1.19. For the Patisiran group, TEAEs of the same SOC and PT but not deemed as associated with premedications were also included in this table.
RR=Relative Risk; OR=Odds Ratio; RD=Risk Difference.
Unstratified RR, OR, and RD were presented.
In estimation of the OR and RR, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the RD.
[1] p-value based on the Wald test testing whether the relative risk equals to 1.
[2] p-value from a logistic regression using the penalized likelihood estimation (the FIRTH option) and with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Table 11.89
Treatment-Emergent Non-severe Adverse Events Associated with Corticosteroid/Premedication Use: Incidence by System Organ Class and Preferred Term
During the 18-Month Treatment Period: Subgroup Analysis
Safety Population

At least 1 AE

Subgroup Statistics	Vutrisiran (HELIOS-A) (N=122) n (%)	Patisiran (HELIOS-A) (N=42) n (%)
Region		
North America, n/N1 (%)	9/ 27 (33.3)	5/ 8 (62.5)
Risk difference (Vutrisiran - Patisiran), (95% CI)	-29.167 (-67.135, 8.802)	
Odds ratio (Vutrisiran/Patisiran), (95% CI)	0.300 (0.058, 1.546)	
Relative risk (Vutrisiran/Patisiran), (95% CI)	0.533 (0.250, 1.137)	
P-value [1]	0.1035	
Western Europe, n/N1 (%)	9/ 42 (21.4)	9/ 20 (45.0)
Risk difference (Vutrisiran - Patisiran), (95% CI)	-23.571 (-48.659, 1.516)	
Odds ratio (Vutrisiran/Patisiran), (95% CI)	0.333 (0.106, 1.051)	
Relative risk (Vutrisiran/Patisiran), (95% CI)	0.476 (0.224, 1.013)	
P-value [1]	0.0541	

TEAE = Treatment-emergent adverse event = AE with onset or worsening in severity after first dose through last dose + 84 days (vutrisiran) or + 28 days (patisiran), or AE considered treatment-related at any time after first dose.
Events were defined as those associated with premedications in CSR Table 14.3.1.19. For the Patisiran group, TEAEs of the same SOC and PT but not deemed as associated with premedications were also included in this table.
RR=Relative Risk; OR=Odds Ratio; RD=Risk Difference.
Unstratified RR, OR, and RD were presented.
In estimation of the OR and RR, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the RD.
[1] p-value based on the Wald test testing whether the relative risk equals to 1.
[2] p-value from a logistic regression using the penalized likelihood estimation (the FIRTH option) and with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Table 11.89
Treatment-Emergent Non-severe Adverse Events Associated with Corticosteroid/Premedication Use: Incidence by System Organ Class and Preferred Term
During the 18-Month Treatment Period: Subgroup Analysis
Safety Population

At least 1 AE

Subgroup Statistics	Vutrisiran (HELIOS-A) (N=122) n (%)	Patisiran (HELIOS-A) (N=42) n (%)
Rest of World, n/N1 (%)	9/ 53 (17.0)	5/ 14 (35.7)
Risk difference (Vutrisiran - Patisiran), (95% CI)	-18.733 (-45.792, 8.325)	
Odds ratio (Vutrisiran/Patisiran), (95% CI)	0.368 (0.100, 1.361)	
Relative risk (Vutrisiran/Patisiran), (95% CI)	0.475 (0.189, 1.194)	
P-value [1]	0.1136	
P-value of Treatment*Region [2]	0.9930	

TEAE = Treatment-emergent adverse event = AE with onset or worsening in severity after first dose through last dose + 84 days (vutrisiran) or + 28 days (patisiran), or AE considered treatment-related at any time after first dose.
Events were defined as those associated with premedications in CSR Table 14.3.1.19. For the Patisiran group, TEAEs of the same SOC and PT but not deemed as associated with premedications were also included in this table.
RR=Relative Risk; OR=Odds Ratio; RD=Risk Difference.
Unstratified RR, OR, and RD were presented.
In estimation of the OR and RR, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the RD.
[1] p-value based on the Wald test testing whether the relative risk equals to 1.
[2] p-value from a logistic regression using the penalized likelihood estimation (the FIRTH option) and with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Table 11.89
Treatment-Emergent Non-severe Adverse Events Associated with Corticosteroid/Premedication Use: Incidence by System Organ Class and Preferred Term
During the 18-Month Treatment Period: Subgroup Analysis
Safety Population

At least 1 AE

Subgroup Statistics	Vutrisiran (HELIOS-A) (N=122) n (%)	Patisiran (HELIOS-A) (N=42) n (%)
Baseline NIS		
<50, n/N1 (%)	18/ 78 (23.1)	18/ 27 (66.7)
Risk difference (Vutrisiran - Patisiran), (95% CI)	-43.590 (-63.679, -23.500)	
Odds ratio (Vutrisiran/Patisiran), (95% CI)	0.150 (0.058, 0.391)	
Relative risk (Vutrisiran/Patisiran), (95% CI)	0.346 (0.213, 0.562)	
P-value [1]	<0.0001	
≥50, n/N1 (%)	9/ 44 (20.5)	1/ 15 (6.7)
Risk difference (Vutrisiran - Patisiran), (95% CI)	13.788 (-3.573, 31.149)	
Odds ratio (Vutrisiran/Patisiran), (95% CI)	3.600 (0.416, 31.121)	
Relative risk (Vutrisiran/Patisiran), (95% CI)	3.068 (0.423, 22.247)	
P-value [1]	0.2674	
P-value of Treatment*Baseline NIS [2]	0.0092	

TEAE = Treatment-emergent adverse event = AE with onset or worsening in severity after first dose through last dose + 84 days (vutrisiran) or + 28 days (patisiran), or AE considered treatment-related at any time after first dose.
Events were defined as those associated with premedications in CSR Table 14.3.1.19. For the Patisiran group, TEAEs of the same SOC and PT but not deemed as associated with premedications were also included in this table.
RR=Relative Risk; OR=Odds Ratio; RD=Risk Difference.
Unstratified RR, OR, and RD were presented.
In estimation of the OR and RR, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the RD.
[1] p-value based on the Wald test testing whether the relative risk equals to 1.
[2] p-value from a logistic regression using the penalized likelihood estimation (the FIRTH option) and with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Table 11.89
Treatment-Emergent Non-severe Adverse Events Associated with Corticosteroid/Premedication Use: Incidence by System Organ Class and Preferred Term
During the 18-Month Treatment Period: Subgroup Analysis
Safety Population

At least 1 AE

Subgroup Statistics	Vutrisiran (HELIOS-A) (N=122) n (%)	Patisiran (HELIOS-A) (N=42) n (%)
Previous Tetramer Stabilizer Use		
Yes, n/N1 (%)	12/ 75 (16.0)	14/ 33 (42.4)
Risk difference (Vutrisiran - Patisiran), (95% CI)	-26.424 (-45.217, -7.631)	
Odds ratio (Vutrisiran/Patisiran), (95% CI)	0.259 (0.102, 0.653)	
Relative risk (Vutrisiran/Patisiran), (95% CI)	0.377 (0.196, 0.725)	
P-value [1]	0.0034	
No, n/N1 (%)	15/ 47 (31.9)	5/ 9 (55.6)
Risk difference (Vutrisiran - Patisiran), (95% CI)	-23.641 (-58.733, 11.452)	
Odds ratio (Vutrisiran/Patisiran), (95% CI)	0.375 (0.088, 1.600)	
Relative risk (Vutrisiran/Patisiran), (95% CI)	0.574 (0.280, 1.178)	
P-value [1]	0.1304	
P-value of Treatment*Previous Tetramer Stabilizer Use [2]	0.6579	

TEAE = Treatment-emergent adverse event = AE with onset or worsening in severity after first dose through last dose + 84 days (vutrisiran) or + 28 days (patisiran), or AE considered treatment-related at any time after first dose.
Events were defined as those associated with premedications in CSR Table 14.3.1.19. For the Patisiran group, TEAEs of the same SOC and PT but not deemed as associated with premedications were also included in this table.
RR=Relative Risk; OR=Odds Ratio; RD=Risk Difference.
Unstratified RR, OR, and RD were presented.
In estimation of the OR and RR, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the RD.
[1] p-value based on the Wald test testing whether the relative risk equals to 1.
[2] p-value from a logistic regression using the penalized likelihood estimation (the FIRTH option) and with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Table 11.89
Treatment-Emergent Non-severe Adverse Events Associated with Corticosteroid/Premedication Use: Incidence by System Organ Class and Preferred Term
During the 18-Month Treatment Period: Subgroup Analysis
Safety Population

At least 1 AE

Subgroup Statistics	Vutrisiran (HELIOS-A) (N=122) n (%)	Patisiran (HELIOS-A) (N=42) n (%)
Genotype		
V30M, n/N1 (%)	11/ 54 (20.4)	11/ 20 (55.0)
Risk difference (Vutrisiran - Patisiran), (95% CI)	-34.630 (-58.935, -10.324)	
Odds ratio (Vutrisiran/Patisiran), (95% CI)	0.209 (0.070, 0.630)	
Relative risk (Vutrisiran/Patisiran), (95% CI)	0.370 (0.191, 0.716)	
P-value [1]	0.0032	
non-V30M, n/N1 (%)	16/ 68 (23.5)	8/ 22 (36.4)
Risk difference (Vutrisiran - Patisiran), (95% CI)	-12.834 (-35.322, 9.654)	
Odds ratio (Vutrisiran/Patisiran), (95% CI)	0.538 (0.192, 1.514)	
Relative risk (Vutrisiran/Patisiran), (95% CI)	0.647 (0.322, 1.302)	
P-value [1]	0.2225	
P-value of Treatment*Genotype [2]	0.2422	

TEAE = Treatment-emergent adverse event = AE with onset or worsening in severity after first dose through last dose + 84 days (vutrisiran) or + 28 days (patisiran), or AE considered treatment-related at any time after first dose.
Events were defined as those associated with premedications in CSR Table 14.3.1.19. For the Patisiran group, TEAEs of the same SOC and PT but not deemed as associated with premedications were also included in this table.
RR=Relative Risk; OR=Odds Ratio; RD=Risk Difference.
Unstratified RR, OR, and RD were presented.
In estimation of the OR and RR, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the RD.
[1] p-value based on the Wald test testing whether the relative risk equals to 1.
[2] p-value from a logistic regression using the penalized likelihood estimation (the FIRTH option) and with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Alnylam Pharmaceuticals Inc.
ALN-TTRSC02-002

Table 11.89
Treatment-Emergent Non-severe Adverse Events Associated with Corticosteroid/Premedication Use: Incidence by System Organ Class and Preferred Term
During the 18-Month Treatment Period: Subgroup Analysis
Safety Population

At least 1 AE

Subgroup Statistics	Vutrisiran (HELIOS-A) (N=122) n (%)	Patisiran (HELIOS-A) (N=42) n (%)
FAP Stage		
I, n/N1 (%)	19/ 84 (22.6)	18/ 31 (58.1)
Risk difference (Vutrisiran - Patisiran), (95% CI)	-35.445 (-54.985, -15.906)	
Odds ratio (Vutrisiran/Patisiran), (95% CI)	0.211 (0.088, 0.508)	
Relative risk (Vutrisiran/Patisiran), (95% CI)	0.390 (0.237, 0.640)	
P-value [1]	0.0002	
II&III, n/N1 (%)	8/ 38 (21.1)	1/ 11 (9.1)
Risk difference (Vutrisiran - Patisiran), (95% CI)	11.962 (-9.407, 33.331)	
Odds ratio (Vutrisiran/Patisiran), (95% CI)	2.667 (0.296, 24.033)	
Relative risk (Vutrisiran/Patisiran), (95% CI)	2.316 (0.324, 16.565)	
P-value [1]	0.4029	
P-value of Treatment*FAP Stage [2]	0.0438	

TEAE = Treatment-emergent adverse event = AE with onset or worsening in severity after first dose through last dose + 84 days (vutrisiran) or + 28 days (patisiran), or AE considered treatment-related at any time after first dose.
Events were defined as those associated with premedications in CSR Table 14.3.1.19. For the Patisiran group, TEAEs of the same SOC and PT but not deemed as associated with premedications were also included in this table.
RR=Relative Risk; OR=Odds Ratio; RD=Risk Difference.
Unstratified RR, OR, and RD were presented.
In estimation of the OR and RR, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the RD.
[1] p-value based on the Wald test testing whether the relative risk equals to 1.
[2] p-value from a logistic regression using the penalized likelihood estimation (the FIRTH option) and with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Table 11.89
Treatment-Emergent Non-severe Adverse Events Associated with Corticosteroid/Premedication Use: Incidence by System Organ Class and Preferred Term
During the 18-Month Treatment Period: Subgroup Analysis
Safety Population

At least 1 AE

Subgroup Statistics	Vutrisiran (HELIOS-A) (N=122) n (%)	Patisiran (HELIOS-A) (N=42) n (%)
Cardiac Subpopulation		
Yes, n/N1 (%)	9/ 40 (22.5)	2/ 14 (14.3)
Risk difference (Vutrisiran - Patisiran), (95% CI)	8.214 (-14.223, 30.652)	
Odds ratio (Vutrisiran/Patisiran), (95% CI)	1.742 (0.328, 9.261)	
Relative risk (Vutrisiran/Patisiran), (95% CI)	1.575 (0.386, 6.426)	
P-value [1]	0.5266	
No, n/N1 (%)	18/ 82 (22.0)	17/ 28 (60.7)
Risk difference (Vutrisiran - Patisiran), (95% CI)	-38.763 (-58.950, -18.576)	
Odds ratio (Vutrisiran/Patisiran), (95% CI)	0.182 (0.072, 0.457)	
Relative risk (Vutrisiran/Patisiran), (95% CI)	0.362 (0.218, 0.599)	
P-value [1]	<0.0001	
P-value of Treatment*Cardiac Subpopulation [2]	0.0262	

TEAE = Treatment-emergent adverse event = AE with onset or worsening in severity after first dose through last dose + 84 days (vutrisiran) or + 28 days (patisiran), or AE considered treatment-related at any time after first dose.
Events were defined as those associated with premedications in CSR Table 14.3.1.19. For the Patisiran group, TEAEs of the same SOC and PT but not deemed as associated with premedications were also included in this table.
RR=Relative Risk; OR=Odds Ratio; RD=Risk Difference.
Unstratified RR, OR, and RD were presented.
In estimation of the OR and RR, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the RD.
[1] p-value based on the Wald test testing whether the relative risk equals to 1.
[2] p-value from a logistic regression using the penalized likelihood estimation (the FIRTH option) and with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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Table 11.89
Treatment-Emergent Non-severe Adverse Events Associated with Corticosteroid/Premedication Use: Incidence by System Organ Class and Preferred Term
During the 18-Month Treatment Period: Subgroup Analysis
Safety Population

At least 1 AE

Subgroup Statistics	Vutrisiran (HELIOS-A) (N=122) n (%)	Patisiran (HELIOS-A) (N=42) n (%)
Weight (kg)		
<65 kg, n/N1 (%)	9/ 46 (19.6)	10/ 15 (66.7)
Risk difference (Vutrisiran - Patisiran), (95% CI)	-47.101 (-73.569, -20.634)	
Odds ratio (Vutrisiran/Patisiran), (95% CI)	0.122 (0.033, 0.445)	
Relative risk (Vutrisiran/Patisiran), (95% CI)	0.293 (0.148, 0.583)	
P-value [1]	0.0005	
>=65 kg, n/N1 (%)	18/ 76 (23.7)	9/ 27 (33.3)
Risk difference (Vutrisiran - Patisiran), (95% CI)	-9.649 (-29.836, 10.538)	
Odds ratio (Vutrisiran/Patisiran), (95% CI)	0.621 (0.238, 1.620)	
Relative risk (Vutrisiran/Patisiran), (95% CI)	0.711 (0.364, 1.387)	
P-value [1]	0.3166	
P-value of Treatment*Weight [2]	0.0603	

TEAE = Treatment-emergent adverse event = AE with onset or worsening in severity after first dose through last dose + 84 days (vutrisiran) or + 28 days (patisiran), or AE considered treatment-related at any time after first dose.
Events were defined as those associated with premedications in CSR Table 14.3.1.19. For the Patisiran group, TEAEs of the same SOC and PT but not deemed as associated with premedications were also included in this table.
RR=Relative Risk; OR=Odds Ratio; RD=Risk Difference.
Unstratified RR, OR, and RD were presented.
In estimation of the OR and RR, a continuity correction of 0.5 was applied to all four cells of 2x2 contingency tables with at least one observed cell of zero count. No continuity correction was applied in calculation of the RD.
[1] p-value based on the Wald test testing whether the relative risk equals to 1.
[2] p-value from a logistic regression using the penalized likelihood estimation (the FIRTH option) and with terms for treatment, the subgroup variable, and the treatment*subgroup interaction.

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UE im Zusammenhang mit der Gabe von Kortikosteroiden/Prämedikationen – Schwere Ereignisse

Für diesen Endpunkt wurden insgesamt weniger als zehn Ereignisse auf Ebene der Gesamtpopulation berichtet. Daher werden, den Vorgaben des G-BA entsprechend, keine Subgruppenanalysen für diesen Endpunkt dargestellt.

UE im Zusammenhang mit der Gabe von Kortikosteroiden/Prämedikationen – Schwerwiegende Ereignisse

Für diesen Endpunkt wurden insgesamt weniger als zehn Ereignisse auf Ebene der Gesamtpopulation berichtet. Daher werden, den Vorgaben des G-BA entsprechend, keine Subgruppenanalysen für diesen Endpunkt dargestellt.