Justification

Gemeinsamer Bundesausschuss

to the Resolution of the Federal Joint Committee (G-BA) on an Amendment of the Pharmaceuticals Directive (AM-RL): Annex XII – Benefit Assessment of Medicinal Products with New Active Ingredients According to Section 35a SGB V Voretigene Neparvovec

of 17 October 2019

Contents

1. Legal basis

According to Section 35a, paragraph 1 German Social Code, Book Five (SGB V), the Federal Joint Committee (G-BA) assesses the benefit of reimbursable medicinal products with new active ingredients.

For medicinal products for the treatment of a rare disease (orphan drugs) that are approved according to Regulation (EC) No. 141/2000 of the European Parliament and of the Council of 16 December 1999, according to Section 35a, paragraph 1, sentence 11, 1st half of the sentence SGB V, the additional medical benefit is considered to be proven through the grant of the marketing authorisation. Evidence of the medical benefit and the additional medicinal benefit in relation to the appropriate comparator therapy need not be submitted (Section 35a, paragraph 1, sentence 11, 2nd half of the sentence SGB V). Section 35a, paragraph 1, sentence 11 1st half of the sentence SGB V thus guarantees an additional benefit for an approved orphan drug, although an assessment of the orphan drug in accordance with the principles laid down in Section 35a, paragraph 1, sentence 3, numbers 2 and 3 SGB V in conjunction with the Chapter 5, Sections 5 et seq. of the Rules of Procedure of the G-BA (VerfO) has not been carried out. In accordance with Article 5, paragraph 8 AM-NutzenV, only the extent of the additional benefit is to be quantified indicating the significance of the evidence.

However, the restrictions on the benefit assessment of orphan drugs resulting from the statutory obligation to the marketing authorisation do not apply if the turnover of the medicinal product with the SHI at pharmacy retail prices and outside the scope of SHI-accredited medical care, including VAT, exceeds € 50 million during the last 12 calendar months. According to Section 35a, paragraph 1, sentence 12 SGB V, the pharmaceutical company must then, within three months of being requested to do so by the G-BA, submit evidence according to Chapter 5, Section 5, subsection 1–6 VerfO, in particular regarding the additional medical benefit in relation to the appropriate comparator therapy as defined by the G-BA according to Chapter 5, Section 6 VerfO and prove the additional benefit in comparison with the appropriate comparator therapy.

In accordance with Section 35a, paragraph 2 SGB V, the G-BA decides whether to carry out the benefit assessment itself or to commission the Institute for Quality and Efficiency in Health Care (IQWiG). On the basis of the statutory requirement in Section 35a, paragraph 1, sentence 11 SGB V that the additional benefit of an orphan drug is deemed to have been proven through the grant of marketing authorisation, the G-BA modified the procedure for the benefit assessment of orphan drugs at its session on 15 March 2012 to the effect that, in the case of orphan drugs, the G-BA initially no longer independently determines an appropriate comparator therapy as the basis for the legally permissible assessment of the extent of an additional benefit to be assumed by law. Rather, the extent of the additional benefit provided by the G-BA is evaluated exclusively on the basis of the approval studies indicating the significance of the evidence.

Accordingly, at its session on 15 March 2012, the G-BA amended the mandate issued to the IQWiG by the resolution of 1 August 2011 for the benefit assessment of medicinal products with new active ingredients in accordance with Section 35a, paragraph 2 SGB V to that effect that, in the case of orphan drugs, the IQWiG is only commissioned to carry out a benefit assessment in the case of a previously defined comparator therapy when the sales volume of the medicinal product concerned has exceeded the legal limit of € 50 million and is therefore subject to an unrestricted benefit assessment (*cf.* Section 35a, paragraph 1, sentence 12 SGB V). According to Section 35a, paragraph 2 SGB V, the assessment must be completed within three months of the relevant date for submission of the evidence and must be published on the internet.

According to Section 35a, paragraph 3 SGB V, the G-BA shall pass a resolution on the benefit assessment within three months of its publication. The resolution is to be published on the internet and forms part of the Pharmaceuticals Directive.

2. Key points of the resolution

The relevant date for the first placing on the market of the active ingredient voretigene neparvovec in accordance with Chapter 5, Section 8, number 1, sentence 2 of the Rules of Procedure of the G-BA (VerfO) is 15 April 2019. The pharmaceutical company submitted the final dossier to the G-BA in accordance with Section 4, paragraph 3, number 1 of the Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with Chapter 5, Section 8, number 1 VerfO on 9 April 2019.

Voretigene neparvovec for the treatment of visual loss due to inherited retinal dystrophy is approved as a medicinal product for the treatment of a rare disease under Regulation (EC) No. 141/2000 of the European Parliament and the Council of 16 December 1999.

According to Section 35a, paragraph 1, sentence 11, 1st half of the sentence SGB V, the additional benefit is considered to be already proven by the marketing authorisation. The extent of the additional benefit is assessed on the basis of the approval studies by the G-BA.

The G-BA carried out the benefit assessment and commissioned the IQWiG to evaluate the information provided by the pharmaceutical company in Module 3 of the dossier on treatment costs and patient numbers. The benefit assessment was published together with the IQWiG assessment on the website of the G-BA (www.g-ba.de) on 15 July 2019, thus initiating the written statement procedure. In addition, an oral hearing was held.

The G-BA has adopted its resolution on the basis of the dossier of the pharmaceutical company, the dossier evaluation carried out by the G-BA, the assessment of treatment costs and patient numbers (IQWiG G19-10) prepared by the IQWiG, and the statements submitted in the written statement and oral hearing procedure.

In order to determine the extent of the additional benefit, the G-BA has evaluated the studies relevant for marketing authorisation with regard to their therapeutic relevance (qualitative) in accordance with the criteria laid down in Chapter 5, Section 5, paragraph 7, sentence 1 numbers 1 through 4 VerfO. The methodology proposed by the IQWiG in accordance with the General Methods [1] was not used in the benefit assessment of voretigene neparvovec.

In the light of the above and taking into account the comments received and the oral hearing, the G-BA has arrived at the following assessment:

2.1 Additional benefit of the medicinal product

2.1.1 Approved therapeutic indication of voretigene neparvovec (Luxturna®) in accordance with the product information

Luxturna is indicated for the treatment of adult and paediatric patients with vision loss due to inherited retinal dystrophy caused by confirmed biallelic *RPE65* mutations and who have sufficient viable retinal cells.

2.1.2 Extent and probability of the additional benefit

In summary, the additional benefit of voretigene neparvovec is assessed as follows:

For adult and paediatric patients with vision loss due to inherited retinal dystrophy caused by confirmed biallelic *RPE65* mutations and who have sufficient viable retinal cells, there is a hint for a considerable additional benefit.

[1] General Methods, Version 5.0 dated 10 July 2017. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen [Institute for Quality and Efficiency in Health Care], Cologne.

Justification:

The benefit assessment is based on the randomised, controlled, multi-centre, open phase III pivotal study 301 for the investigation of voretigene neparvovec compared with a monitoring wait-and-see approach. The study included 31 patients (intervention group N = 21, control group N = 10; corresponds to the ITT population) with confirmed diagnosis of Leber's congenital amaurosis (LCA) because of mutations in the *RPE65* gene. In the study, the inclusion of patients from ≥ 3 years was planned. Patients in the intervention arm each received 1.5×10^{11} vector genome voretigene neparvovec as a gene therapeutic intervention in the form of a sub-retinal injection under anaesthesia; after application in the first eye (Day 0A; maximum 90 days after baseline) the injection in the second eye (Day 0B) was performed non-simultaneously within 12 ± 6 days after application in the first eye (Day 0A; maximum 90 days after baseline). A change of patients from the control group to the intervention arm was possible after one year at the earliest provided that the patients still fulfilled the inclusion and exclusion criteria of the study at that time. According to the study protocol, the observation period after injection of the test medication into the second eye was 1 to 1.5 years in both groups. Following Study 301, the patients were monitored for up to 15 years in the single-arm Extension Study 302.

The patients in study 301 were randomised at a ratio of 2:1 stratified by age (≥ 10 vs < 10 years) and outcome level of the mobility test during screening with the worse eye (passing at ≥ 125 vs < 125 lux). The primary endpoint of the study was the change in the multi-luminance mobility test (MLMT), measured bilaterally after Year 1T (= Year 1 after treatment of the second eye in the intervention group) and Year 1C (= Year 1 after the baseline of the control group) between the treatment groups.

In addition to the evaluations of the pivotal, comparative RCT 301, the pharmaceutical company also presented the results of Extension Study 302 for the benefit assessment. Although the significance of the study is limited because of the one-armed study design and methodological limitations, for the primary endpoint MLMT, the descriptive results are taken into account in the benefit assessment in order to make an initial assessment of the sustainability of the effects of voretigene neparvovec. In Study 302, the efficacy and safety endpoints defined in Study 301 were further evaluated. It remains unclear to what extent the survey was conducted analogously to Study 301. At the beginning of Extension Study 302, patients of the original control group in study 301 received the test product. For the most recent data cut-off of 5 March 2017, data are available for the original intervention group for Year 3 after baseline (3 years after administration of the test medication) and for the original control group, for Year 2 after injection of the test medication.

Mortality

In Study 301, mortality was recorded as a safety endpoint in the survey of adverse events. No deaths were reported during the study.

Morbidity

Functional vision using multi-luminance mobility test (MLMT)

The Multi-Luminance Mobility Test (MLMT) is used to measure changes in functional vision, in particular the ability to orient oneself in an obstacle course under different lighting conditions and to move independently. The test uses seven standardised illuminances from 1 lux to 400 lux, which are checked with calibrated light meters at five different positions on the obstacle course. The investigators assessed the result level of the mobility test using a predefined combination of speed and precision at a given illuminance level, which could be between 1 and 400 lux. The illuminance at which the patient was able to pass the mobility test in the corresponding test situation with concealed/uncovered eye was decisive for mobility. This lux value was then converted into a mobility test score between 6 and −1 for each test situation. A higher score corresponds to better mobility.

Orientation ability or visual function under different ambient lighting conditions is regarded as patient-relevant. In Study 301, the analysis of the change in the MLMT mobility score for both eyes (bilateral) at Year 1T/C compared with baseline between treatment groups was defined as the primary endpoint. For the MLMT at Year 1, there is a statistically significant advantage in favour of neparvovec compared with a monitoring wait-and-see approach (difference of the observed mean changes: 1.6 [95% CI 0.7; 2.4]; $p < 0.001$). No patient under voretigene neparvovec performed the test worse at Year 1 than at baseline.

The pharmaceutical company also submitted evaluations based on an assumed Minimal Important Difference (MID) of 1 point. The responder analyses submitted for MID of 1 point could not be taken into account for methodological reasons. SMDs calculated *post hoc* according to Hedges' g were submitted with the written statement; for the MLMT, this is completely outside the irrelevance range of −0.2 to 0.2 (SMD 1.50 (95% CI: [0.66; 2.34]). There is thus a statistically significant, clinically relevant advantage for voretigene neparvovec compared with a monitoring wait-and-see approach.

Because of the open study design, the risk of bias at the subjective endpoint is considered high. Thus, knowledge of the treatment assignment may have influenced the performance of the test by the patient. Nevertheless, the assessment of the test was blinded, quality assurance measures were applied during the study, and the test was carried out in a standardised manner. Uncertainties also remain regarding, among other things, the increased proportion of procedural deviations in the test procedure (intervention group). In addition, a ceiling effect could be observed because of the already high baseline values in the mobility score. Regardless of the methodological limitations mentioned above, for the endpoint MLMT, there is statistically significant, clinically relevant advantage for voretigene neparvovec compared with a monitoring wait-and-see approach.

In Study 302, changes to baseline were reported for the MLMT endpoint. The purely descriptive, non-comparative data for the change from baseline for the original intervention and control group up to Round 3 and Round Year 2 are of an order of magnitude similar to that of Study 301.

Light Sensitivity by full-field light sensitivity threshold test (FST)

In Study 301, the full-field light sensitivity threshold test (FST) was used to measure full-field sensitivity.

The objective of this test is to record the subjective light sensitivity of the entire visual field in which the test subject can still see. For this purpose, patients are exposed to different luminance levels (brightness) in order to assess the perception of the patient with regard to the luminance of a flash of light. In Study 301, a whole-field electroretinogram (ERG) was used to determine the luminance of a light flash that the test subject can still see. White, red, and blue light stimuli were tested individually for each eye. An algorithm identified the minimum luminance (brightness) at which the test subject reliably perceived light. The luminance was converted to a logarithmic value. For log10 (cd s/m^2), a more negative result corresponds to a lower threshold value and thus an improved light sensitivity, thereby indicating an improved photoreceptor function.

From a methodological point of view it is noted that the subjective tests could be measured several times until acceptable reliability values were achieved. The SOP describes criteria for assessing reliability. However, this approach is nevertheless viewed critically in view of the open study design. The decision to repeat the test was therefore not taken systematically but rather at the subjective discretion of the investigator. For the final assessment of the risk of bias, there is no information on how often repeated measurements took place in the respective treatment arms. Because of the open study design and the lack of blinding in the evaluation of the FST, the risk of bias is regarded as high. According to the pharmaceutical company, the statistical analyses were based on the ITT population. The cause of the missing data in the measurement with blue and red light (for three patients in the intervention group or one patient in the control group) is unclear.

Sensitivity to light is assessed as patient-relevant. For the FST, there are statistically significant effects in favour of voretigene neparvovec compared with a monitoring wait-and-see approach for white, blue, and red light. Moreover, the results are comparable for all three light variants and remain consistent throughout the entire course of the study up to Year 1 after baseline. The SMD calculated post hoc according to Hedges' g exclusively for the test measured with white light is also completely outside the irrelevance range of −0.2 to 0.2.

Visual acuity using ETDRS/HOTV eye chart

In the study, visual acuity was assessed using either the ETDRS or the HOTV eye chart depending on the cognitive abilities of the child. The ETDRS chart was used for 18 individuals in the intervention group and 8 individuals in the control group. The HOTV chart was used for 3 individuals the intervention group and 1 individual in the control group.

Visual acuity is a patient-relevant endpoint. The results of the analyses defined *a priori* in which both eye charts (ETDRS, HOTV) were evaluated together were not statistically significant between the treatment groups at Year 1 and are consistent throughout the study up to Year 1 after baseline. It remains unclear to what extent the two eye charts are interchangeable. The results are therefore limited in their informative value. Separate analyses for both eye charts separately were not performed. Because of the open study design and the lack of blinding in the evaluation, the risk of bias is regarded as high.

For the written statement, *post hoc* responder analyses for a MID of ≥ 10 letters were submitted separately for both the ETDRS and the HOTV eye charts. Responder analyses for an improvement or deterioration by ≥ 15 letters or deterioration by ≥ 10 letters were not submitted. Data on the validity of a MID of 10 or 15 letters for the HOTV chart could not be identified.

In total, 6 persons in the intervention group (n = 18 using the ETDRS table) had an improvement of ≥ 10 letters when using the ETDRS table. However, this was not the case for any person in the control group. There is no statistically significant difference between the treatment groups.

Visual field measured by perimetry according to Goldmann and Humphrey

In study 301, both static (according to Humphrey) and kinetic (according to Goldmann) examination methods were used to measure the visual field. Both perimetry methods are widely used in clinical practice to measure the visual field. Goldmann perimetry covers the entire visual field, whilst Humphrey perimetry focuses on specific regions in the visual field. An extension of the visual field defect or visual field restrictions are considered patient-relevant.
With the static examination method used here (Humphrey), the stimuli are located at a fixed position in the visual field to be examined, and the light intensity of the stimuli is varied. With the Goldmann kinetic investigation method, on the other hand, the intensity remains constant and the stimuli are mobile. They are moved from outside the visual field into the presumed visual field, and the place of the first perception is documented. Different stimuli were used for the two perimetric methods.

From a methodological point of view, it is critically noted that no concrete information is available on the frequency with which subjective tests are carried out or on the repeatability of baseline measurements. The statistical analysis procedure was also only described *post hoc* in the study report or Module 4. For the final assessment of the risk of bias, there is no information on how often repeated measurements took place in the respective treatment arms. Because of the open study design and the lack of blinding in the evaluation of both methods of perimetry, the risk of bias is regarded as high.

Because the test medication is applied to a specific region (macula) of the eye, for Humphrey perimetry, functional differences in this region were investigated before and after application of the test medication. Because application in the fovea region was to be avoided, an investigation was also carried out in this region. In the dossier the results were averaged over both eyes for the light sensitivity limit in the unit decibel for the macula and fovea area. For Humphrey's perimetry, a statistically significant result for the average macular threshold in favour of voretigene neparvovec was shown in the macular region. The post-hoc SMD calculated according to Hedges' g was also completely outside the irrelevance range of −0.2 to 0.2. In the area of the fovea, no statistically significant difference could be derived.

For the Goldmann perimetry, the V4e stimuli were used (size: 64 mm^2, brightness: 315 cd/m^2) and III4e (size: 4 mm^2, brightness: 315 cd/m^2) were used. Except for 5 patients in the control group for year 1, results for both stimuli (V4e and III4e) were mapped for Goldmann perimetry. The study planned to collect baseline data for both stimuli together. Because of the low number of patients (< 70% each) in the intervention (n = 11) and control group (n=5), the results for stimulus V4e are not presented. In Study 301, Goldmann perimetry showed a statistically significant, clinically relevant difference for the overall score of Stimulus III4e in favour of voretigene neparvovec.

Overall, for both methods of perimetry in Study 301, statistically significant effects in favour of voretigene neparvovec compared with a monitoring wait-and-see approach were observed. Based on the Hedges' g evaluations, these are assessed as clinically relevant.

Quality of life

Visual Function Questionnaire

In Study 301, health-related quality of life was assessed using the Visual Function Questionnaire. It is an instrument developed in orientation to the validated disease-specific quality of life questionnaire NEI VFQ-25. Thus, the questions of the two questionnaires differ considerably in their wording. Answer options and the structure of the questionnaire were also changed compared with the NEI VFQ-25. The pharmaceutical company submitted only validation studies for the NEI VFQ-25. Because of the considerable differences, neither a transferability of the psychometric properties nor the MID from the NEI VFQ-25 to the newly developed Visual Function Questionnaire seems possible. The evaluations cannot be taken into account within the framework of the benefit assessment.

Side effects

AE, SAE, discontinuation because of AE

In Study 301, SAE and severe AE occurred only in the intervention group. The proportion of individuals with AE ≥ grade 3 was higher in the intervention group than in the control group. In Study 301, neither the number of patients with AE nor the number of patients with severe AE, SAE, and therapy discontinuations because of AE differ significantly between treatment with voretigene neparvovec and a monitoring wait-and-see approach.

It should be noted that in the intervention group – contrary to the control group and the usual procedure of simultaneous surveying – AE were not reported from baseline but rather only from the first injection, which took place on average 34.3 days after randomisation. Thus, no AE were evaluated for this period. According to the information submitted with the written statement, the average observation period in the intervention group was 406.6 days from the first injection to one year after the second injection. In the control group, the average period between baseline and Year 1 was 354.8 days. The difference between the two groups was about 50 days.

Because the small number of cases, the reliability of data of the results is limited. In addition, because of the open study design, the risk of bias for the safety endpoints can be assessed as high.

Overall assessment

For the treatment of adult and paediatric patients with vision loss due to inherited retinal dystrophy caused by confirmed biallelic *RPE65* mutations and who have sufficient viable retinal cells, results on mortality, morbidity, quality of life, and side effects are available based on the pivotal Phase III RCT 301. Initial results from the one-arm Extension Study 302 on the long-term efficacy and safety effects of voretigene neparvovec over 2 and 3 years are also available.

In the mortality category, no deaths occurred in Study 301.

In the morbidity category, there are statistically significant, clinically relevant advantages in favour of voretigene neparvovec for the patient-relevant endpoints MLMT (functional vision/orientation), FST (light sensitivity), and perimetry (visual field); a statistically significant change in visual acuity was not observed for voretigene neparvovec compared with a monitoring wait-and-see approach.

For quality of life, there are no suitable data for the benefit assessment.

In the endpoint category side effects, there are currently no statistically significant differences between the comparator arms.

The evaluations of the Extension Study 302 (data cut-off of 5 May 2017) indicate that the positive effects in MLMT achieved in Study 301 under voretigene neparvovec are maintained in their order of magnitude even 2 to 3 years after administration. A final assessment of the effects is currently not possible. Neither can any statements be made with sufficient certainty on the sustainability of the changes achieved under voretigene neparvovec.

In summary, the statistically significant and clinically relevant advantages of voretigene neparvovec compared with a monitoring wait-and-see approach with respect to the endpoints MLMT, FST, and perimetry in the overall view are classified as considerable.

Reliability of data (probability of additional benefit)

The assessment of the additional benefit is based on the randomised, controlled, multi-center, open Phase III pivotal study 301, which investigated the efficacy and safety of voretigene neparvovec compared with a monitoring wait-and-see approach. Results of the ongoing Extension Study 302 were also presented.

For Study 301, the risk of bias is classified as high at the study level. In addition to the open study design, the lack of blinding in the execution and evaluation of the endpoints can contribute to a bias of the results, especially in the case of subjective endpoints. The risk of bias at the endpoint level is considered high for all endpoints collected with subjective tests. This applies in particular to the patient-relevant endpoints light sensitivity (using FST), visual field (using perimetry), and visual acuity (using ETDRS/HOTV eye chart). For the FST in particular, the test was not repeated according to systematic guidelines but rather subjectively at the discretion of the investigator. For the endpoints FST and perimetry, there are considerable uncertainties with respect to operationalisation, especially regarding the repeatability of the subjective tests.

In addition, the possible influence of the natural development of children and adolescents on the performance of the tests remains unclear.

Based on this study, no statement can be made on the sustainability of the effects. The evaluations presented in Extension Study 302 also do not currently allow statements to be made on this with sufficient certainty. The significance of Extension Study 302 is limited, among other things, because of the one-arm study design and methodological limitations.

Uncertainties also remain regarding the operationalisation of the criterion “sufficiently viable retinal cells” used in Study 301. In addition, no data are available on the safety and efficacy of voretigene neparvovec in patients under 4 years of age.

In the overall view, the reliability of data provides a hint for an additional benefit.

2.1.3 Limitation of the period of validity of the resolution

The limitation of the period of validity of the resolution on the benefit assessment of voretigene neparvovec has its legal basis in Section 35a, paragraph 3, sentence 4 SGB V. Thereafter, the G-BA may limit the validity of the resolution on the benefit assessment of a

medicinal product. In this case, the limitation is justified by objective reasons consistent with the purpose of the benefit assessment according to Section 35a, paragraph 1 SGB V.

To assess the additional benefit of voretigene neparvovec in the treatment of adult and paediatric patients with vision loss due to inherited retinal dystrophy caused by confirmed biallelic *RPE65* mutations and who have sufficient viable retinal cells, the pharmaceutical company presents the results of the pivotal Phase III RCT 301 study, which investigates voretigene neparvovec compared with a monitoring wait-and-see approach.

The evaluations presented within the framework of this benefit assessment procedure do not currently permit a conclusive assessment of the additional benefit for voretigene neparvovec with sufficient certainty, in particular because of the lack of long-term data on all patient-relevant endpoints. Without long-term data, the sustainability of the positive effect of gene therapy cannot be assessed. The long-term effects of gene therapy with voretigene neparvovec, in particular with regard to the safety profile, are currently the subject of further investigations within the framework of the conditions for marketing authorisation. The results of the Phase III Study 301 or the ongoing single-arm Extension Study 302 must be submitted to the EMA no later than Q4 2031. The EMA has also commissioned the pharmaceutical company with a PASS register study on long-term safety. These safety data as well as the results of the long-term observational study, are also relevant for the benefit assessment in accordance with Section 35a SGB V. To evaluate these relevant data for the treatment of adult and paediatric patients with vision loss due to inherited retinal dystrophy with voretigene neparvovec at patient-relevant endpoints, it is considered sufficient to limit the period of validity of this resolution to 31 December 2021.

For the renewed benefit assessment after the deadline, long-term data on patient-relevant endpoints – the interim analysis of Extension Study 302 for all patient-relevant endpoints and the safety data of the registry – must be submitted in order to assess the sustainability of the effects in the dossier. The G-BA considers a deadline of 31 December 2021 to be appropriate.

The possibility that a benefit assessment for the medicinal product voretigene neparvovec can be carried out for other reasons (*cf* Chapter 5, Section 1, paragraph 2 VerfO) remains unaffected by this.

In accordance with Section 3, number 5 AM-NutzenV in conjunction with Chapter 5, Section 1, paragraph 2, number 7 VerfO, the procedure for the benefit assessment for the medicinal product voretigene neparvovec shall recommence when the deadline has expired. For this purpose, the pharmaceutical company must submit a dossier to the G-BA at the latest on the date of expiry to prove the extent of the additional benefit of voretigene neparvovec in relation to the appropriate comparator therapy (Section 4, paragraph 3, no. 5 AM-NutzenV in conjunction with Chapter 5 Section 8, no. 5 VerfO).

2.1.4 Summary of the assessment

The present assessment concerns the benefit assessment of the medicinal product Luxturna® with the active ingredient voretigene neparvovec.

This assessment refers to the therapeutic indication “treatment of adult and paediatric patients with vision loss due to inherited retinal dystrophy caused by confirmed biallelic *RPE65* mutations and who have sufficient viable retinal cells”.

For the benefit assessment, the pharmaceutical company presents the results of the pivotal Phase III RCT 301, which provides the basis for marketing authorisation and allows comparative statements to be made for voretigene neparvovec compared with a monitoring wait-and-see approach. The first results of the one-armed Extension Study 302 over 2 and 3 years are also available; these were additionally considered for the primary endpoint of orientation capability (MLMT).

In the morbidity category, there are statistically significant, clinically relevant advantages in favour of voretigene neparvovec in the endpoints MLMT (functional vision/orientation), FST (light sensitivity), and perimetry (visual field); a statistically significant change in visual acuity was not observed for voretigene neparvovec compared with a monitoring wait-and-see approach. For quality of life, there are no suitable data for the benefit assessment. In the endpoint category side effects, no statistically significant differences between the comparator arms can be derived at present.

The significance of the two studies presented is classified as limited. This is due, among other things, to the respective study design and the existing uncertainties with regard to the subjective tests used to assess morbidity and their repeatability. No reliable statements can be made on the sustainability of the positive effects based on the studies available.

In the overall view, for the treatment of adult and paediatric patients with vision loss due to inherited retinal dystrophy caused by confirmed biallelic *RPE65* mutations and who have sufficient viable retinal cells, a hint for a considerable additional benefit of voretigene neparvovec compared with a monitoring wait-and-see approach can be derived. Because of pending study results, the resolution will be limited until 31 December 2021.

2.2 Number of patients or demarcation of patient groups eligible for treatment

The information on the number of patients is based on the target population in statutory health insurance (SHI).
These are based on the data from the pharmaceutical company’s dossier. The figures are based on prevalence data of patients with Leber’s congenital amaurosis (LCA) and retinitis pigmentosa (RP), each with biallelic *RPE65* mutations; taking into account the lowest and highest prevalence, the range is from the minimum and maximum proportion of 188 to 655 patients (mean of 355 patients). In the next step, the minimum and maximum proportion of treatable patients are taken into account; the resulting patient population of approx. 100 to 530 patients results from the approved therapeutic indication, which is restricted to those patients with “sufficiently viable retinal cells”. The calculation of the size of the target population is in a plausible order of magnitude in the overall view but is nevertheless subject to uncertainties.

2.3 Requirements for a quality-assured application

A. Regulatory requirements for marketing authorisation

The requirements in the product information are to be taken into account. The European Medicines Agency (EMA) provides the contents of the product information (summary of

product characteristics, SmPC) for Luxturna® (active ingredient: voretigene neparvovec) at the following publicly accessible link (last access: 8 October 2019): https://www.ema.europa.eu/documents/product-information/luxturna-epar-product-information_de.pdf

Treatment with voretigene neparvovec must be performed by retinal surgeons experienced in performing macular surgery.

In accordance with the specifications of the European Medicines Agency (EMA) regarding additional measures for risk minimisation, the pharmaceutical company must provide training material for medical professionals (e.g. retinal surgeons and pharmacists) and a patient ID card. The training material contains, in particular, instructions for the preparation and implementation of the intraocular, subretinal application of voretigene neparvovec in an operating field under anaesthesia.
The Risk Management Plan (RMP) stipulates that the training material for healthcare professionals should contain relevant information on the preparation, storage, and use of voretigene neparvovec, including a description of the materials and subretinal administration.

Qualification and availability of medical and non-medical staff

In order to minimise the safety risks associated with treatment with voretigene neparvovec, it should be ensured that treatment facilities preparing and administering the voretigene neparvovec treatment meet the criteria approved by the EMA, which is to be implemented in accordance with the risk management plan. The staff involved in the administration (i.e. vitreoretinal surgeons and pharmacists) have participated in a compulsory training programme on the use of voretigene neparvovec to ensure the correct use of voretigene neparvovec and thus minimise the risks (increased intraocular pressure, retinal tear, macular diseases, cataract, intraocular inflammation and/or infection associated with the procedure and retinal detachment, transmission through third parties) associated with its administration and/or the administration procedure.

The criteria for treatment centres should include the following:

- Presence of a specialist ophthalmologist with expertise in the care and treatment of patients with hereditary retinal dystrophy.
- Presence or affiliation with a retinal surgeon experienced in subretinal surgery and qualified to administer voretigene neparvovec.
- An anti-inflammatory medication should be prescribed in accordance with the product information.
- The interval for treatment of the second eye should be planned according to the product information.

B. Further requirements for the quality-assured application of voretigene neparvovec in qualified treatment facilities

According to the current state of medical knowledge, the following requirements for the implementation of treatment should be considered in addition to the requirements in the product information and of the European Medicines Agency (EMA) with regard to additional risk minimisation measures:

Indication before the therapy is carried out

All of the following conditions should be met prior to therapy with voretigene neparvovec:

- The diagnosis of retinal dystrophy is clinically proven.
- Sequence variants homozygous or compound heterozygous biallelic in the gene *RPE65* are verified as the cause of disease. Ideally, proof should be provided by segregation analysis of the parents.
- It is ensured that sufficient target cells are available to ensure therapeutic benefit.
- The patient and, if necessary, the legal guardians were individually informed about the natural course of the disease, the prognosis of the planned therapy, and the risk profile of the therapy as well as about any other therapies.

Implementation of the therapy

All of the following clinical conditions should be met when conducting therapy with voretigene neparvovec:

- In particular, the doctor should have experience with vitrectomies in the respective age group of the patients. For the treatment of children, the doctor should have experience in paediatric ophthalmology.
- The doctor should also have experience in subretinal surgery in patients with advanced retinal dystrophy or other degenerative diseases of the retina.
- An accumulation of Luxturna™ in the vitreous cavity and thus the risk of lower bioavailability in the target tissue and/or higher systemic biodistribution should be avoided.
- If children are treated, an anaesthetist experienced in paediatric anaesthesia should be available.

All of the following technical conditions should be met when conducting therapy with voretigene neparvovec:

- The formal training for the preparation and surgical application of voretigene neparvovec by the manufacturer has been completed.
- The equipment for regular storage and preparation of the injection solution is available.
- The active ingredient is stored at temperatures below −60°C until application, and the cold chain is guaranteed.
- Voretigene neparvovec is prepared for use under aseptic conditions and in a sterile manner by trained staff using dual control.
- The entire surgical team is trained in handling substances of biological protection level 1.
- The application corresponds to the specifications of the manufacturer or the company selling the product.
- The disposal of the virus solution and the surface disinfection of the operating theatre is carried out according to the local regulations as well as the current recommendations of the Robert Koch Institute.
- Availability of a pharmacy capable of processing and manufacturing AAV vector-based gene therapy products.

After-care

All of the following conditions should be met in the after-care of patients after treatment with voretigene neparvovec:

- All side effects are recorded in a registry study.
- The treatment of complications is carried out by the initial treating physician or with his/her involvement.
- The clinical examination and testing of visual functions are performed under standardised conditions.
- In order to assess the success of the therapy, at least the best corrected visual acuity and global retinal sensitivity (FST) as well as OCT and FAF scans should be performed pre-operatively and post-operatively.

The regulations according to Section 136a SGB V remain unaffected by this.

2.4 Treatment costs

The treatment costs are based on the contents of the product information and the information listed in the LAUER-TAXE® (last revised: 1 October 2019).

Luxturna is intended for single administration into a single eye[2]. The medicinal product is administered as a single dose of 1.5×10^{11} vector genomes (Vg) to each eye after a vitrectomy as a subretinal injection. The treatment of both eyes is performed on different days within a short time interval of at least 6 days.

Treatment period:

Designation of the therapy	Treatment mode	Number of treatments/patient/year	Treatment duration/treatment (days)	Treatment days/patient/ year
Medicinal product to be assessed				
Voretigene neparvovec	Single dose; 1 × per eye on different days	2	1	2

[2] An inpatient application is assumed.

Usage and consumption:

Designation of the therapy	Dosage	Dose/patient/treatment days	Consumption by potency/treatment day	Treatment days/ patient/ year	Annual average consumption by potency
Medicinal product to be assessed					
Voretigene neparvovec	1.5×10^{11} vector genome (Vg)	1.5×10^{11} Vg	$1 \times 1.5 \times 10^{11}$ Vg	2	$2 \times 1.5 \times 10^{11}$ Vg

Costs:

Voretigene neparvovec is listed in the LAUER-TAXE® but is only sold as a hospital pack[2]. The active ingredient is therefore currently not subject to the Pharmaceutical Price Ordinance, and there are no rebates according to Section 130 or Section 130a SGB V. The calculation is based on the purchase price of the clinic package plus 19% value added tax. This differs from the information usually taken into account in LAUER-TAXE®.

Furthermore, costs are incurred for the pre- and postoperative immunomodulatory treatment with prednisone recommended by the product information.

Costs of the medicinal product:

Designation of the therapy	Package size	Cost (purchase price of clinic pack plus value added tax)
Medicinal product to be assessed		
Voretigene neparvovec	1 injection solution	€ 410,550

Pharmaceutical retail price (LAUER-TAXE®) as last revised: 1 October 2019

Costs for additionally required SHI services:

Only costs directly related to the use of the medicinal product are taken into account. If there are regular costs for the necessary medical treatment or the prescription of other services when using the drug to be evaluated in accordance with the product information, the costs incurred for this must be taken into account as costs for additionally required SHI services.

Medical treatment costs, medical fee services, and costs incurred for routine examinations (e.g. regular laboratory services such as blood count tests) that do not exceed standard expenditure in the course of the treatment are not shown.

Voretigene neparvovec is applied by subretinal injection after previous vitrectomy. The procedure is currently performed on an inpatient basis in specialised centres. For the pars plana vitrectomy to be performed prior to the administration of voretigene neparvovec, the

inpatient costs are stated. The calculation is based on the valuation ratio of the DRGs C15Z (0.804) multiplied by the Federal Base Rate 2019 (€ 3,544.97).

According to the product information a pre- and postoperative immunomodulatory treatment with prednisone is recommended. This is displayed below for children and adults. The initiation of the immunomodulatory treatment plan is recommended 3 days before administration of voretigene neparvovec to the first eye; for the second eye, this should follow the same treatment plan and replace the treatment plan for the first eye.
In principle, the G-BA does not base the calculation of the consumption of weight-dependent medicinal products to be dispensed on indication-specific average weights. Therefore, for the body weight, the mean weight of an adult (77.0 kg) according to the official representative statistic "Microcensus 2017" is assumed[3]. For children, the average weight is 36.79 kg (< 1 year to < 18 years). A range from the minimum (6 days between administration in both eyes) and maximum (>16 days between administration in both eyes) duration of the regime, which depends on the time interval between administration of voretigene neparvovec in the first and second eye, is used as a basis for the calculation. As a result, the same costs arise for the time-limited immunomodulatory treatment with prednisone, taking into account the ranges mentioned, regardless of age and treatment regimen (for each pack of 50 tablets).

Designation of the therapy	Package size	Costs (pharmacy wholesale price)	Rebate Section 130 SGB V	Rebate Section 130a SGB V	Costs after deduction of statutory rebates
Medicinal product to be assessed					
Pre- and postoperative immunomodulatory treatment with prednisone[4]	50 Tablets	€ 20.58	€ 1.77	€ 0.76	€ 18.05

Pharmaceutical retail price (LAUER-TAXE®) as last revised: 1 October 2019

As a result of a voretigene neparvovec application, further costs arise in the outpatient area because of the necessity for control examinations. At the time of the decision, part of the pre- and postoperative controls (e.g. optical coherence tomography (OCT)) cannot be calculated using the uniform rating scale (EBM). The resulting costs are thus non-quantifiable.

The obligation of the evaluation committee to decide on an adjustment of the uniform rating scale for medical services in accordance with Section 87, paragraph 5b, sentence 5 SGB V remains unaffected by the failure to present the costs insofar as the product information on the medicinal product provides for mandatory services for its application.

Costs are incurred for the diagnostic investigations and control examinations carried out. The frequency and type of examination used may vary from patient to patient. The resulting costs

[3] Statistisches Bundesamt [German Federal Office for Statistics]. Microcensus 2017: Questions on health; body measurements of the population 2017 [online]. 2 August 2018 [Accessed: 11 September 2018]. URL: https://www.destatis.de/DE/Publikationen/Thematisch/Gesundheit/Gesundheitszustand/Koerpermasse5239003179004.pdf?__blob=publicationFile

[4] Fixed amount

cannot be quantified because of the individual determination of the control intervals by the treating physician, among other things.

Designation of the therapy	Description of the service	Cost per application	
Medicinal product to be assessed			
Voretigene neparvovec	Vitrectomy, including subretinal injection	Pars plana vitrectomy, including sub-retinal injection [5,6] (Operation and procedure keys (OPK) Codes: 5–158.01, 5–156.0, 5–156.9)	approx. € 2,850 per eye
	Check-up examinations	Non-quantifiable	Non-quantifiable

3. Bureaucratic costs

The proposed resolution does not create any new or amended information obligations for care providers within the meaning of Annex II to Chapter 1 VerfO and, accordingly, no bureaucratic costs.

4. Process sequence

On 9 April 2019, the pharmaceutical company submitted a dossier for the benefit assessment of voretigene neparvovec to the G-BA in due time in accordance with Chapter 5, Section 8, number 1, sentence 2 VerfO.

The benefit assessment of the G-BA was published on 15 July 2019 together with the IQWiG assessment of treatment costs and patient numbers on the G-BA website (www.g-ba.de), thus initiating the written statement procedure. The deadline for submitting written statements was 5 August 2019.

The oral hearing was held on 26 August 2019.

In order to prepare a recommendation for a resolution, the Subcommittee on Medicinal Products commissioned a working group (Section 35a) consisting of the members nominated by the leading organisations of the care providers, the members nominated by the SHI umbrella organisation, and representatives of the patient organisations. Representatives of the IQWiG also participate in the sessions.

The evaluation of the written statements received and the oral hearing were discussed at the session of the subcommittee on 8 October 2019, and the proposed resolution was approved.

At its session on 17 October 2019, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

[5] The cost of subretinal injection is based on inpatient treatment and billing via DRG code C15Z, which includes a pars plana vitrectomy.
[6] The costs for an inpatient procedure are shown as follows.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee Medicinal product	9 July 2019	Knowledge of the benefit assessment of the G-BA
Working group Section 35a	13 August 2019	Information on written statements received; preparation of the oral hearing
Subcommittee Medicinal product	26 August 2019	Conduct of the oral hearing
Working group Section 35a	3 September 2019 17 September 2019 1 October 2019	Consultation on the dossier evaluation by the G-BA, the assessment of treatment costs and patient numbers by the IQWiG, and the evaluation of the statement procedure
Subcommittee Medicinal product	8 October 2019	Concluding discussion of the proposed resolution
Plenum	17 October 2019	Adoption of the resolution on the amendment of Annex XII of the AM-RL

Berlin, 17 October 2019

Federal Joint Committee (G-BA)
in accordance with Section 91 SGB V
The chair

Prof Hecken