Protocol Title: Comparative Effectiveness of Roctavian to Standard of Care Hemostatic Therapies in Germany Among People with Severe Hemophilia A: A Prospective Non-Interventional Study Utilizing Data Collected in the German Hemophilia Register.

Short Title / Study Name: Comparative Effectiveness of Roctavian to Standard of Care

Protocol Number: 270-603

Study Phase: IV

Sponsor Name(s) and Address: BioMarin International Limited, Shanbally Ringaskiddy, County Cork, Ireland P43 R298

Sponsor Contact:

[redacted]
BioMarin Deutschland GmbH
Westerbachstr. 28, 61476 Kronberg/Ts.
[redacted]

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PROTOCOL SYNOPSIS

<table>
<tr><td>Protocol Number</td><td colspan="2">270-603</td></tr>
<tr><td>Title of Study</td><td colspan="2">Comparative Effectiveness of Roctavian to Standard of Care Hemostatic Therapies in Germany Among People with Severe Hemophilia A: A Prospective Non-Interventional Study Utilizing Data Collected in the German Hemophilia Register.</td></tr>
<tr><td>Phase and Type of Study</td><td colspan="2">Phase IV non-interventional prospective study, to compare the effectiveness of Roctavian to the Standard of Care (SoC) hemostatic prophylaxis therapies</td></tr>
<tr><td rowspan="9">Study Objectives and Endpoints</td><td colspan="2">The aim of this non-interventional study is to evaluate the overall effectiveness and safety of Roctavian compared to SoC hemostatic prophylaxis treatment for (PwSHA).
The study objectives and endpoints below will compare Roctavian and SoC prophylaxis treatment with coagulation factor VIII (FVIII) or emicizumab, unless otherwise noted.</td></tr>
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• On-demand hemostatic treatments.</td></tr>
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• Haemo-Quality of Life assessment (QoL-A).
• Brief Pain Inventory-Short Form (BPI-SF).</td></tr>
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• Adverse events leading to hospitalization or death.
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</table>

	• To describe time to resumption of prophylactic treatment among patients administered Roctavian.	• Resumption of prophylactic hemostatic treatments.
Study Duration	Q1 2024 to Q3 2028	
Study Population	Adult PwSHA without a history of (or current) inhibitors to FVIII in Germany.	
Sample Size	Approximately 70 PwSHA in the Roctavian cohort and approximately 330 PwSHA in the SoC cohorts.	
Medicinal Products	Roctavian. Hemostatic prophylaxis treatments: FVIII replacement therapies or emicizumab.	
Summary of Eligibility Criteria	Adult (≥18 years old) male PwSHAs registered in the German Hemophilia Register (DHR) database administered Roctavian or hemostatic prophylaxis during the study identification window with FVIII or emicizumab with no history of (or current) FVIII inhibitor.	

Data Elements of Interest	Key data elements to compare or describe outcomes in the Roctavian and SoC Cohorts include:
	• Bleeding Events
	• SoC Hemostatic Treatment Usage
	• Clinical Outcome Assessment Tools
	  ○ Hemophilia Quality of Life assessment (Haemo-QoL-A)
	  ○ Hemophilia Joint Health Score (HJHS)
	  ○ Brief Pain Inventory-Short Form (BPI-SF)
	• Safety Events	

Statistical Analysis	Comparison of outcomes between the Roctavian and SoC cohorts after propensity score adjustment for differences in baseline characteristics (eg, demographic and clinical variables recorded in the DHR prior to the index date).	

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2 LIST OF ABBREVIATIONS

Abbreviation	Definition
AAV	Adeno-associated virus
AAV5	Adeno-associated virus serotype 5
AbD	Anwendungsbegleitende Datenerhebung
ABR	Annual bleeding rate
ACT	Appropriate comparative therapy
ADR	Adverse drug reaction
AE	Adverse event
AIR	Annualized infusion/injection rate
BMI	Body mass index
BPI-SF	Brief Pain Inventory-Short Form
BW	Body weight
CI	Confidence interval
CIOMS	Council for International Organizations of Medical Sciences
DHR	German Hemophilia Register
EHL	Extended half- life
FVIII	Coagulation factor VIII
G-BA	Federal Joint Committee
HA	Hemophilia A
HCP	Health care practitioners
HCV	Hepatitis C Virus
hFVIII	Human coagulation factor VIII
HJHS	Hemophilia Joint Health Score
HTC	Hemophilia Treatment Center
ICF	Informed consent form
IgG	Immunoglobulin G
IPTW	Inverse probability of treatment weight
ITT	Immune tolerant therapy
IU	International units
MCID	Minimal clinically important differences
PEG	Polyethylene glycol
PRO	Patient reported outcome
PS	Propensity score

PSM	Propensity score matching
PwSHA	People with severe hemophilia A
QoL-A	Quality of Life assessment
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SD	Standard deviation
SHL	Standard half- life
SMD	Standardized mean difference
SMRW	Standardized mortality ratio weighting
SoC	Standard of Care

3 RATIONALE AND BACKGROUND

3.1 Background

3.1.1 Severe Hemophilia A

Hemophilia A (HA) is an X-linked recessive bleeding disorder that affects approximately 1 in 5,000 males (Iorio 2019), (Soucie 2020). It is caused by mutations in the factor VIII (FVIII) gene that codes for FVIII protein, an essential cofactor in the coagulation pathway. The clinical phenotype of people with HA (PwHA) is largely governed by the level of residual FVIII expression. Severe HA is classified as FVIII activity less than 1% of wild-type (< 1 international units (IU)/dL), moderate disease comprises 1-5% of wild-type activity and the mild form is 5-40% activity. The clinical manifestations of severe HA remain frequent spontaneous bleeding episodes, predominantly in joints and soft tissues, with a substantially increased risk of death from hemorrhage when the brain is involved. Bleeding into joints can cause acute pain and swelling and can result in reduced range of joint motion, long-term cartilage damage and debilitating hemophilic arthropathy (Wyseure 2011). Early use of prophylaxis is recommended following diagnosis of HA to maintain joint health and prevent joint destruction (Manco-Johnson 2014). However, despite the use of prophylaxis many patients still experience joint bleeds which may lead to joint deterioration over time (Oldenburg 2015). Furthermore, not all bleeds may be clinically evident, as there are indications of subclinical bleeds in patients receiving treatment for their hemophilia (Manco-Johnson 2007). In addition to the risk of experiencing a bleeding event, prophylaxis poses a substantial treatment burden on individual patients. Most PwHA in Germany use FVIII substitution as their prophylactic regimen with 2-3 intravenous injections per week. PwHA additionally have the option of prophylaxis with non-factor therapies, such as the bispecific antibody treatment emicizumab, which is taken once per week to once every 4 weeks (Dtsch Arztebl Int. 2019).

3.1.2 Benefit Assessment for Valoctocogene Roxaparvovec

Valoctocogene roxaparvovec is a gene therapy medicinal product that expresses the B-domain deleted SQ form of human coagulation factor VIII (hFVIII-SQ). It is delivered by a one-time intravenous infusion.

It was approved by the European Commission on 24 August 2022 for the following indication: treatment of severe HA (congenital factor VIII deficiency) in adult patients without a history of factor VIII inhibitors and without detectable antibodies to adeno-associated virus serotype 5 (AAV5).

According to § 35a of the German Social Code, Book Five (SGB V), the Federal Joint Committee (G-BA) evaluates the additional benefit of reimbursable medicinal products with new active ingredients, and pharmaceutical companies are obliged to submit a dossier on product benefit when a new product is launched on the German market or authorized for new indications. The purpose of early benefit assessment in Germany is to compare newly authorized drugs to an appropriate comparative therapy in order to establish a ruling on their additional benefit, which serves as the basis for price negotiations between the manufacturer and the National Association of Statutory Health Insurance Funds (GKV-Spitzenverband). On 16 March 2023, the G-BA ruled that there is "Hint for a non-quantifiable additional benefit" for valoctocogene roxaparvovec (Federal Joint Committee 2023).

3.1.3 Routine Data Collection and Evaluations for Valoctocogene Roxaparvovec

3.1.3.1 G-BA resolutions and procedures

On 02 February 2023 the G-BA requested the Routine Data Collection and Evaluations (generally referred to as the AbD in this protocol) according to § 35a paragraph 3b SGB V for Valoctocogene Roxaparvovec (AM-RL 2023). The resolution was preceded by a G-BA resolution of 03 February 2022 (AM-RL 2022) which initiated the procedure as well as a concept development by the Institute for Quality and Efficiency in Health Care (Institut fur Qualität und Wirtschaftlichkeit im Gesundheitswesen, IQWiG) on 30 September 2022 (AM-RL 2022).

Along with the resolution mandating Routine Data Collection and Evaluations, G-BA passed a resolution restricting authority to provide care to those providers who participate in the required data collection. This only takes effect with the start of the data collection accompanying the application, which is determined in a separate decision (AM-RL 2023a).

3.1.4 Compared Therapies

3.1.4.1 ROCTAVIAN®

Valoctocogen roxaparvovec (ROCTAVIAN®) is indicated for the treatment of severe hemophilia A (congenital factor VIII deficiency) in adult patients without a history of factor VIII inhibitors and without detectable antibodies to AAV5 (BioMarin Intl. Ltd. 2022). Factor VIII (FVIII) is a domain protein composed of Sections A1-A2, B, A3, and C1-C2. In the activated form of FVIII, the B domain is cleaved. ROCTAVIAN is a gene therapy based on an adeno-associated virus (AAV) vector that acts as a gene delivery vehicle. The vector is replication incompetent and consists of an AAV serotype 5 capsid containing a transgene encoding a variant of human coagulation factor VIII in which the B domain has been replaced by a 14 amino acid long (SQ) linker sequence (hFVIII-SQ) (Bunting 2018). After a

single intravenous administration, the vectors introduce the transgenes into liver cells and episomes are formed in the nucleus. As a result, the cells begin continuous production of FVIII. Hemostasis is thus restored in the treated patients.

3.1.4.2 Factor VIII substitution

FVIII concentrates derived from human plasma or manufactured by recombinant technologies in cell culture can be used for haemostatic prophylaxis. The half-life of FVIII in plasma is 10 to 12 hours. Therefore, it is necessary to inject plasmatic or standard half-live FVIII concentrates at least 3 times per week. Factor drugs with extended half-lives can reduce injection frequency or increase trough levels. Various techniques are used to delay clearance, such as fusion techniques or pegylation (covalent binding of polyethylene glycol (PEG) at particular points on the FVIII molecule). Fusion involves other recombinant proteins, such as the Fc domain of immunoglobulins, which have a substantially longer half-life in the blood and protect against early degradation. The half-life of FVIII is limited by binding to von Willebrand factor. For the dosing frequency to be reduced from 3 times to twice per week while maintaining coagulation factor levels, the half-life needs to be at least 1.3 times that of a standard FVIII drug (Miesbach 2019).

The list of approved factor VIII products used in Germany for the prophylactic treatment of severe HA can be found on the website of the Paul-Ehrlich-Institute (Paul Ehrlich Institute 2023b).

3.1.4.3 Emicizumab

Emicizumab is a bispecific humanized monoclonal antibody. In Germany, it was authorized on 13 March 2019 for patients with severe HA and no inhibitors, of any age, at a dose of 1.5 mg/kg body weight (BW) once weekly, 3 mg/kg once every 2 weeks, or 6 mg/kg BW once every 4 weeks (with a loading dose of 3 mg/kg BW per week for 4 weeks in all cases) (Sampei 2018).

3.2 Rationale

This study is being undertaken to fulfill the G-BA requirement for Routine Data Collection and Evaluations (as described in Section 3.1.3.1). Specifically, this study will provide data on the comparative effectiveness of Roctavian to standard of care (SoC) hemostaticprophylaxis treatments (see Sections 3.1.4.2 and 3.1.4.3) among people with severe HA (PwSHA) without a history of FVIII inhibitors. Safety will also be described (and compared if warranted) among these populations to understand potential differences.

4 STUDY OBJECTIVES AND ENDPOINTS

The aim of this non-interventional study is to evaluate the overall effectiveness and safety of Roctavian compared to SoC hemostatic prophylaxis treatments for PwSHA.

The specific objectives are listed below. All objectives will compare Roctavian and SoC with FVIII or emicizumab, unless otherwise noted.

Table 1: Objectives and Endpoints

Objectives	Endpoints
Primary	
• To compare the annualized bleeding rate for treated bleeds.	• Bleeding events requiring treatment with exogenous FVIII
Secondary	
• To compare the annualized bleeding rate for major, life threating, and joint bleeds.	• Major bleeding events • Life-threatening bleeding events • Bleeding events occurring in the joint
• To compare the proportion of patients with zero bleeds for treated, major, life threating, and joint bleeds.	• Bleeding events requiring treatment with exogenous FVIII • Major bleeding events • Life-threatening bleeding events • Bleeding events occurring in the joint
• To compare the use of hemostatic medications.	• Prophylactic hemostatic treatments • On-demand hemostatic treatments

• To compare joint health, quality of life, and pain.	• Hemophilia Quality of Life assessment (Haemo-QoL-A) • Hemophilia Joint Health Score (HJHS) • Brief Pain Inventory-Short Form (BPI-SF)
• To compare safety events of interest.	• All cause death • Hemophilia-related death • Adverse events leading to hospitalization or death • Targeted adverse events of development of FVIII inhibitors, thromboembolic events, new malignant neoplasms, and severe liver disease (liver failure or cirrhosis)
• To describe time to resumption of prophylactic treatment among patients administered Roctavian.	• Resumption of prophylactic hemostatic treatments

5 STUDY METHODS

5.1 Study Design

This non-interventional cohort study will enroll adult PwSHA treated in routine clinical practice with either Roctavian or SoC hemostatic prophylaxis treatment with FVIII replacement therapies or emicizumab in Germany. Study participants will be followed based on data prospectively entered into the German Hemophilia Register (DHR). All participants are expected to have previously enrolled in the DHR due to local regulations. Study participants will consent for their data that is collected in the DHR to be utilized for this study, consistent with the requirements of the AbD. Participants will provide consent during a study identification window beginning in Q1 2024 and ending in Q3 2025. This study identification window will allow for 3 years of follow-up for each participant in the DHR prior to the data cut required to report on the study for the purposes of the AbD (report due Q1 2029).

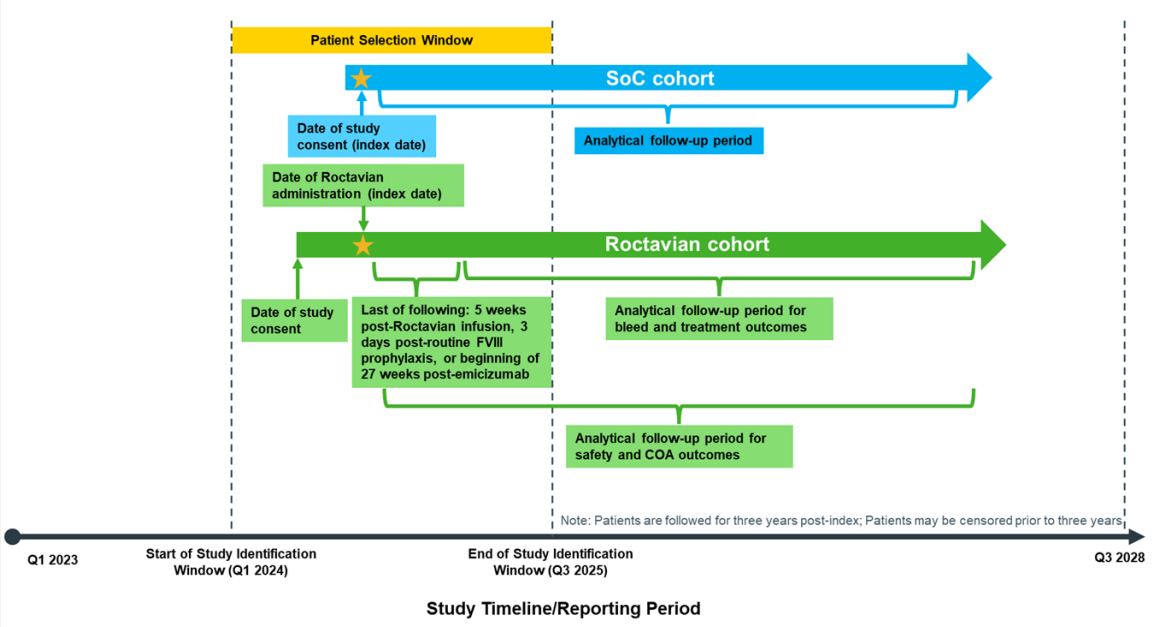
During the study identification window, participants will be assigned to a study cohort based on the treatment that was received during the identification window. All participants receiving Roctavian during the identification window will be assigned to the Roctavian Cohort. Participants receiving SoC hemostatic prophylaxis treatment only during the identification window will be assigned to the SoC Cohort. Index date will be defined as the date of Roctavian administration for PwSHA treated with Roctavian (Roctavian Cohort) and the date of consent for PwSHA treated with SoC products (SoC Cohort). Participants will be followed for 3 years after index date (follow-up period) based on data extracted from the DHR. If a participant in the SoC Cohort subsequently receives Roctavian during follow-up after the identification period, their data will be censored for analysis at the time of Roctavian administration. Study participants will be followed consistent with the Study Elements of Interest (see Section 7.1). The study aims to enroll at least 70 PwSHA into the Roctavian Cohort and at least 330 PwSHA into the SoC Cohort. The study is anticipated to complete in Q3 2028. The study completion date is based on allowing time to analyze data and submit a report per the AbD defined deadline of February 2029. Changes to the AbD defined deadlines for the report would result in changes to the study completion timeframe, as well as the identification window described above.

The Roctavian and SoC Cohorts will be compared based on events observed during the follow-up period regarding bleeding events, use of hemostatic medication, clinical outcome assessments measuring joint health, quality of life, pain and safety (hemophilia-related death, adverse events leading to hospitalization and death, and targeted adverse events of FVIII inhibitor development, thrombotic events and new malignancies). PwSHA in Germany are

generally seen at a Hemophilia Treatment Center every 6 months and therefore it is expected that clinical outcome assessments on joint health, quality of life and pain would be assessed at those timepoints.

Comparisons of safety will be conducted if warranted by the number of events observed. The occurrence of and time to resumption of prophylactic hemostatic therapy will also be described among the Roctavian Cohort during the follow-up period. The Roctavian and SoC Cohorts will be compared after propensity score (PS) adjustment for differences in baseline characteristics (eg, demographic and clinical variables recorded in the DHR prior to the index date). These characteristics will also be used to describe the cohorts and to inform the PS. Exact variable included in the PS will be based on statistical, as well as clinical associations, between baseline characteristics and the likelihood of receiving the gene therapy. Variables included in the PS along with the PS adjustment method will be selected after the cohorts are described.

Figure 1 Study Schema



5.2 Study Population

Adult PwSHA and without a history of inhibitors to FVIII in Germany will be identified from the DHR (see Section 7.2.1 for further description of the DHR). Study participants can be treated with either Roctavian or SoC hemostatic prophylaxis treatments (FVIII replacement treatments or emicizumab). Approximately 70 PwSHA and 330 PwSHA are expected to be enrolled in the Roctavian and SoC Cohorts respectively. The therapeutic

treatment strategy for an individual who consents to this study is made independently of the decision to participate in the study and enrollment into this study will not inform the treatment strategy.

Study participants will consent to have their individual patient data recorded in the DHR consistent with the AbD as described in the data elements of interest (Section 7.1) and extracted for the purposes of this study.

Additional criteria for participation in the study are provided in Section 5.2.1 and 5.2.2.

5.2.1 Inclusion Criteria

Individuals are eligible to be included in the study if all of the following criteria apply:

- Male PwSHA as recorded in the DHR
- ≥18 years of age at index date
- Treatment with Roctavian or SoC hemostatic prophylaxis therapies during the identification window
    - Participant administered commercially available Roctavian. Note: Assignment of a therapeutic strategy is not determined by this protocol.
        - OR
    - Has received prophylactic treatment with FVIII or Emicizumab for at least 12 months prior to study entry.
- Participant (or their legally authorized representative, if appropriate) has provided written, signed informed consent for participation in the study

5.2.2 Exclusion Criteria

Subjects are excluded from the study if any of the following criteria apply:

- Is currently in, or previously participated (in the last 12 months before index), an interventional clinical trial involving an investigational product to treat HA
- History of inhibitors against FVIII ever (or current) as recorded in the DHR prior to index

6 SUBJECT ENROLLMENT

Before subjects are enrolled into the study, BioMarin requires a copy of the site's written independent ethics committee/institutional review board/research ethics board (IEC/IRB/REB) approval of the protocol, informed consent form and all other subject information and/or recruitment material, if applicable. All subjects, or their legally authorized representative (if applicable), must sign and personally date the consent form before the collection of any study specific data. All subjects who enter the study will be assigned a unique subject identification number.

This number will be used to identify the subject throughout the study and must be used on all study documentation related to that subject.

Subjects are considered enrolled when they have signed the consent in this study.

All participants fulfilling the inclusion/exclusion criteria will be included in the study. As the study is being conducted in a real-world observational setting, the actual numbers of participants per population (SoC/Roctavian) cannot be controlled.

7 DATA COLLECTION

Data collected for this study will be recorded in the DHR consistent with existing local regulations for data entry frequency. For participants in this study (study is the same as the AbD), physicians will be expected to enter data utilizing the DHR annual forms with reporting periods relative to the index date (to meet the requirements of the AbD).

7.1 Overview of Data Collection

All data for this study will be collected and stored in the DHR. Study site personnel are responsible for patient data collection and data entry into the DHR.

Table 2 specifies the data collection elements of interest to be collected for this study as they occur in accordance with the standard clinical care consistent with the AbD.

Data entered into the DHR must be documented in subject medical records (source documents). Baseline data will be derived based on information entered into the DHR prior to index date. Further detail on data fields within the DHR (if available at the time of protocol drafting) that will be used for both baseline and follow-up data are described further in Sections 7.2.3, 7.2.4, and 7.2.5.

Table 2: Data Elements of Interest

Variables	Baseline Data (prior to index)	At index	Data entered as observed after index	End of Follow-up (3 years post index)
Demographic and Disease Information				
Documentation of hemophilia disease and severity	X			
Demographics, including height and weight	X	X		
Inhibitor Status	X		X	X
Clinical Trial Participation	X[a]		X	
Comorbidities of interest	X			
Bleeding Events, Hemostatic Treatment Usage, & Gene Therapy Information				
Bleeding Events	X[a]		X	X
SoC Hemostatic Treatment Usage	X[a]		X	X
Gene Therapy Information		X[c]		
AAV Testing Information	X	X		
Use of immunosuppression for gene therapy		X[c]	X[c]	
FVIII Activity Levels			X[c]	
Clinical Outcome Assessments				
Haemo-QoL-A questionnaire	During baseline or Index[d]	During baseline or Index[d]	Bi-Annually[e]	At end of study period or subject discontinuation[f]

Hemophilia Joint Health Score (HJHS)	During baseline or Index[d]	During baseline or Index[d]	Bi-Annually[e]	At end of study period or subject discontinuation[f]
BPI-SF	During baseline or Index[d]	During baseline or Index[d]	Bi-Annually[e]	At end of study period or subject discontinuation[f]
Safety Information				
Death			X	At subject discontinuation[g]
Hemophilia-related death			X	At subject discontinuation[g]
Adverse events leading to hospitalization or death			X	At end of study period or subject discontinuation[g]
Thromboembolic events			X	At end of study period or subject discontinuation[g]
Severe liver disease (liver failure or cirrhosis			X	At end of study period or subject discontinuation[g]
New malignant neoplasms			X	At end of study period or subject discontinuation[g]

AAV, Adeno-associated virus; BPI-SF, Brief Pain Inventory-Short Form; FVIII, factor VIII; HJHS, Hemophilia Joint Health Score, QoL-A, quality of life assessment; SoC, standard of care.

General footnotes

a. Based on data recorded in the DHR for the 12 months prior to index
b. Non-mandatory field reported during a DHR reporting period (start/end date of reporting period as defined by HTC entering data). Data requested to be entered for all AbD participants for reporting periods relative to the index date (e.g., reporting period starting with the index date)
c. Recorded for the Roctavian cohort only
d. Non-mandatory field in the DHR. Assessment requested to be completed for all AbD participants on index or the 60 days prior to index and entered into the DHR consistent with routine clinical management of a patient.
e. Non-mandatory field in the DHR. Assessment requested to be completed for all AbD participants entered into the DHR approximately every 6 months during follow-up consistent with routine clinical management of a patient.
f. Non-mandatory field in the DHR. Assessment requested to be completed for all AbD participants entered into the DHR at end of follow-up (approximately 3 years after the index date) consistent with routine clinical management of a patient or at the time of discontinuation.
g. Mandatory field in the DHR (see variable tables below regarding fields that are anticipated to be added to the DHR). Data requested to be entered at the end of the study period (approximately 3 years after the index date) or at time of subject discontinuation.

7.1.1 Baseline Data Collection

Baseline data will be derived from data entered into the DHR prior to or at the index date, or to be entered at the index date reflecting annual reporting into the DHR for the time period prior to the index date. Data variables and relevant data collection fields as described below

in Table 3 and Table 4 (see Section 7.2.3) will be utilized to describe the study populations (Roctavian Cohort and SoC Cohort), as well as utilized to inform the propensity scores. Specific time periods for baseline variables are defined in the Table 3 and Table 4 (see Section 7.2.3).Variables described in Table 5 (see Section 7.2.4) related to gene therapy will be utilized to describe the Roctavian Cohort only, as the variables are specific to gene therapy.

7.1.2 Ongoing Data Collection

Data is expected to be entered into the DHR consistent with existing practices at study sites and applicable local regulations. It is expected that data will be entered into the DHR on an annual basis at a minimum, though may be more frequent if entered after each visit to an HTC. Data on ongoing events (see Table 6, Table 7, and Table 8, as well as the descriptions in sub-sections to Section 7.2.4) will be entered into the DHR after the index date for a period of 3 years for each participant (based on the index date for that participant).

7.1.3 Study Completion

The study will be completed in approximately Q3 2028 after the last patient consented has data entered into the DHR for the 3-year study period. For an individual study participant, the study will complete 3 years after a participants index date (or events listed in section 8.1). The final study completion will be dependent on the conditions of the AbD (see Section 5.1).

For participants who withdraw from the study (see Section 8.1 for detail on study withdrawal), initiate participation in a clinical trial, and/or initiate gene therapy (if in the SoC Cohort after the identification period), physicians will enter data for the variables ‘Data entered as observed after index’ or ‘End of Follow-up’ as described in Table 2.

7.2 Description of Data Elements of Interest and Source

7.2.1 Data Source

The data source is a clinical registry maintained by the Paul-Ehrlich-Institute, in cooperation with the Gesellschaft für Thrombose- und Hämostaseforschung e. V. (GTH), the Deutsche Hämophiliegesellschaft zur Bekämpfung von Blutungskrankheiten e. V. (DHG) and the Interessengemeinschaft Hämophiler e. V. (IGH), under the name “Deutsches Hämophilieregister” (DHR).

It is a registry for medical research and quality assurance in the care of persons with the diseases hemophilia A, hemophilia B, von Willebrand syndrome or other coagulation factor deficiencies. Medical data of patients with hemostasis disorders are compiled in the DHR. It

has been in operation since December 2008. About 130 institutions report data from a total of almost 8,500 affected persons every year (Paul Ehrlich Institute 2023a).

As a clinical patient registry, it represents a systematic collection of data, ie, standardized medical documentation, which makes data more comparable and thus evaluable in order to answer questions relevant to practice. As hemophilia is a rare disease, a registry is of particular importance: large-scale studies are often difficult to conduct in this field, as there are simply not enough patients to make reliable statements. Therefore, the strength of a registry lies in the possibility of long-term observation of the disease and its treatment in order to be able to draw meaningful conclusions.

The legislator has recognized this and, with an extension of the Transfusion Act (TFG), has given the German Hemophilia Registry a special status with a legal basis. Data collection in the DHR is now mandatory and all treating physicians are obliged to inform their patients about participation in the DHR.

7.2.2 Description of Data Elements of Interest

Relevant data elements for study participants are described below (see Sections 7.2.3, 7.2.4).

As the study will utilize data that is collected in the DHR, relevant data fields will be utilized in data extracts from the DHR wherever possible. Certain data fields to collect data elements as specified/requested for the AbD will be added or modified in the DHR. A full list of the data fields utilized in the study analysis, inclusive of fields added to the DHR (when available) and operational definitions of variables, will be maintained in the Statistical Analysis Plan (SAP). Specific definitions for variables, along with other derived variables, may be refined based on observations of the raw data, which will not become available till after this study is initiated (eg, based on the initial data cut). Additional derived variables and specific definitions will be provided in the SAP and described in interim and final reports.

7.2.3 Demographic Information and Clinical History

Demographic information, comorbid conditions and clinical history will be derived from data entered into the DHR prior to and/or at index date. These variables will be utilized to identify and describe the study cohorts, as well as being considered for inclusion in the PS. Variables collected in the DHR (at the time of protocol drafting) that will be utilized to characterize the study cohorts regarding demographic information, location of hemophilia management and participation in clinical trials are describe in Table 3, with variables to characterize participants clinical history, including hemophilia history, described in Table 4.

Table 3: Demographic Information

Variable	Description	Currently captured in DHR	Time period for Analysis	Entry into DHR	Operational notes including Relevant Data Fields in DHR
Age	Approximate age of participant	✓	At index	At enrollment	Date of birth (month/year) collected in DHR, but only year is available for analysis. - Inclusion criteria of aged ≥18 years of age at index to be captured through consent. - Study participants will be described based on categorial intervals for year of birth (5-year increments). - An assumed day and month of birth (eg, 1 July) for all participants will be implemented to describe approximate age of subjects at index.
Gender	Male gender	✓	--	At enrollment	Confirm inclusion criteria.
Height	Height in cm	✓ (see operational note)	At index or during baseline	Ongoing	Description of cohort, based on recording closest to or at index Field is not a required field in the DHR, therefore there is an increased chance of missing data. Physicians for participants enrolling into the AbD will be asked to ensure that this data is entered into the dataset.
Weight	Weight in kg	✓ (see operational note)	At index or during baseline	Ongoing	Description of cohort, based on recording closest to or at index Field is not a required field in the DHR, therefore there is an increased chance of missing data. Physicians for participants enrolling into the AbD will be asked to ensure that this data is entered into the dataset.
Body mass index (BMI)	Body mass index in kg/m^2	X	At index or during baseline	--	Description of cohort, based on recording closest to or at index Derived based on height and weight recorded in DHR. (See note above regarding variables required to derive BMI.)

Variable	Description	Currently captured in DHR	Time period for Analysis	Entry into DHR	Operational notes including Relevant Data Fields in DHR
Hemophilia Treatment Center (HTC)	Primary HTC/institution managing a patient	X	At index	Ongoing	N/A HTC primarily managing a participant will provided in a deidentified form based on HTC identifier collected in the DHR.
Clinical trial participation	Participation in an interventional clinical trial involving an investigational product to treat Hemophilia A	✓	At index and/or during baseline	Ongoing after enrollment	Exclusion criteria. - Derived based participation ever or currently in a clinical trial in the DHR with entry and/or withdrawal dates indicating enrollment in the 12 months prior to index or current enrollment at index. - Clinical trial name (free text field) to be utilized to specifically exclude interventional trials, if feasible. If not feasible, any clinical trial will be excluded. - Participation in the AbD and/or the non-interventional studies of Roctavian will not result in exclusion. See Section 10.3 for detail on use of this variable to censor data.

AbD, Anwendungsbegleitende Datenerhebung; BMI, Body mass index; DHR, German Hemophilia Register; HTC, Hemophilia Treatment Center

Table 4: Clinical History, including Hemophilia History

Variable	Description	Currently captured in DHR	Time period for Analysis	Entry into DHR	Operational notes including Relevant Data Fields in DHR
Hemophilia History					
Diagnosis	Hemophilia A diagnosis	✓	--	At enrollment	Inclusion criteria Based on diagnosis recorded in DHR as Hemophilia A
Hemophilia Severity	Severe Hemophilia	✓	--	At enrollment	Inclusion criteria Based on severity recorded in DHR as severe
Age at diagnosis	Age at Hemophilia A diagnosis	✓	--	At enrollment	Description of cohorts Derived based on date of diagnosis and year of birth record in DHR, unless date of diagnosis is recorded as 'unknown'.
Age at first FVIII factor administration	Age of first FVIII administration	✓	--	At enrollment	Description of cohorts Derived based on date of first FVIII administration and year of birth record in DHR, unless date of administration is recorded as 'unknown'.
History of or current inhibitors	Any history of or current inhibitors	✓	At index or any time prior to index	At enrollment & ongoing	Exclusion criteria Based on recording of the DHR variables for inhibitors developed before the patient started treatment at the current treatment center, positive inhibitor tests after enrollment in the DHR, or use of immune tolerant therapy (ITT). Exclusion will be based upon either 2 positive inhibitor tests (regardless of occurrence before or after enrollment in DHR) or 1 positive inhibitor tests (regardless of occurrence before or after enrollment in DHR) and use of ITT.

Variable	Description	Currently captured in DHR	Time period for Analysis	Entry into DHR	Operational notes including Relevant Data Fields in DHR
Target joints	Presence of target joints	✓ (see operational note)	At index and/or during baseline	Ongoing	Description of cohorts. The DHR does not currently record the number or location of target joints, though the presence of a target joint can be derived based on therapy usage recorded in the DHR for bleeding with the bleeding location identified as 'target joint'. Updated to the DHR data collection forms may allow for further description of target joints beyond presence or absence of a target joint. If updates do occur, any additional variables (or derivation of variables) regarding target joints will be documented in the SAP. Note: Target joint is defined based on the discretion of the physician recording the data in the DHR and does not necessarily adhere to the ISTH definition for a target joint.
Bleeding History					
Bleeding history	Bleeding events in the 12 months prior to index	✓	Baseline	Ongoing	Description of cohorts based in annualized bleeding rates. See Table 6 for further description of bleed types recorded in the DHR. Derived based on therapy usage recorded in the DHR for suspected, spontaneous, traumatic, or unknown cause of bleeding.
Treatment History					
Use of prophylaxis	Hemostatic prophylaxis for at least the 12 months prior to index	✓	Baseline	Ongoing	Inclusion criteria Derived based on the therapy usage recorded in the DHR. Participants required to have reported use of a therapy for 'prophylaxis' in each of the 12 months prior to index.

Variable	Description	Currently captured in DHR	Time period for Analysis	Entry into DHR	Operational notes including Relevant Data Fields in DHR
Prophylaxis type	Medication class utilized for prophylaxis	✓	Baseline	Ongoing	Description of cohort. - Derived based on the therapy usage recorded in the DHR for 'prophylaxis'. Including (but not limited to) description of the use of: - FVIII only (any, standard half-life (SHL) products only, extended half-life (EHL) products only, SHL & EHL) - Non-factor products only (eg, emicizumab) - FVIII and non-factor products
FVIII Consumption	Total FVIII consumption during the 12 months prior to index	✓	Baseline	Ongoing	Description of cohort. Derived based on reported FVIII consumption for each therapeutic use of FVIII, reported for different prophylaxis types. Will be described based on total FVIII utilized in international units (Ius), as well as, IU/kg based on availability of weight data (see note in Table 3).
Infusion Rate	Number of infusions during the 12 months prior to index	✓	Baseline	Ongoing	Description of cohort. Providing data allows, derived based on the therapy usage and frequency of during individual usage periods recorded in the DHR for any reason. Data is expected to be able to allow for summaries of annualized infusion/injection rate (AIR).
Comorbidities					
Hepatitis C Virus (HCV) status	History of and/or current HCV, along with current status of infection	✓	Any time prior to index	Ongoing	Description of cohorts. Based on HCV status recorded in the DHR, including but not limited to: History of HCV (active/cured infection vs no infection history) Active vs cured infection for those with a history Active infection during baseline Treatment for HCV eradication during baseline
Chronic liver disease status	Presence of liver fibrosis and/or cirrhosis	✓	Baseline	Ongoing	Description of cohorts. Based on liver disease (eg, report of fibrosis or cirrhosis) recorded in the DHR.

Variable	Description	Currently captured in DHR	Time period for Analysis	Entry into DHR	Operational notes including Relevant Data Fields in DHR
Other comorbid diseases	Other diseases recorded in the DHR	✓ (see operational note)	At index, during baseline, and/or any time prior to index	Ongoing	Description of cohorts (if feasible). Based on recording of 'other diseases' in the DHR and free text specification disease. Reporting of other diseases, categorization of diseases, and use of variable for analyses (eg, inclusion in a PS) will be based upon actual data recorded. Due to the free text nature of the field and potential differential reporting between sites, data collected may not be analyzable.

AbD, Anwendungsbegleitende Datenerhebung; AIR, Annualized infusion/injection rate; BMI, Body mass index; DHR, German Hemophilia Register; EHL, Extended half- life; FVIII, Coagulation factor VIII; HCV, Hepatitis C Virus; HTC, Hemophilia Treatment Center; ISTH, International Society on Thrombosis and Haemostasis; ITT, Immune tolerant therapy; IU, International units; PS, Propensity score; SAP, Statistical Analysis Plan; SHL, Standard half-life

7.2.4 Gene Therapy Administration

For the Roctavian Cohort only, details of gene therapy administration including the use of immunosuppression will be described (see Table 5) at or around the index date. Variables in Table 5 are only expected to be recorded for PwSHA administered a gene therapy, therefore will not be considered for inclusion in the PS. If variables regarding gene therapy administration beyond those variables collected in the DHR at the time of protocol drafting are added to the DHR, these variables will also be described and detailed in changes to the SAP. Further, if variables are consistently collected for both the Roctavian Cohort and SoC Cohort (such as AAV antibody information), these variables may be considered for the PS based on observations of the data at the time of data cuts.

Table 5: Gene Therapy Administration Variables

Variable	Description	Currently captured in DHR	Time period for Analysis	Entry into DHR	Operational notes including Relevant Data Fields in DHR
Date of gene therapy	Date of Roctavian administration	✓	Index	At administration	Utilized to Identify the index date for the Roctavian Cohort Utilized as the date for censoring analyses (when applicable), see Section 10.3
AAV Antibody testing	Serostatus for AAV 5 antibodies	✓	Index	At/around time of administration	Derived from AAV testing being conducted and result of positive/negative. Note: Current DHR dataset (at time of protocol drafting) does not specify exact testing method utilized, nor AAV type. Therefore, spurious 'positive' findings may be recorded. Eg, AAV 6 antibody presence, which is not relevant for eligibility for Roctavian.
Use of any immuno-suppression	Use of any immuno-suppression	✓	Index and during follow-up	At administration and ongoing	Note: Current DHR dataset (at time of protocol drafting) only records immunosuppression type (eg, corticosteroids) as a free text field, which is not anticipated to be analyzable.
Duration of immuno-suppression	Duration of immuno-suppression after administration	✓	Index and during follow-up	At administration and ongoing	Derived based on start and end dates for immune-suppression.

AAV, Adeno-associated virus; DHR, German Hemophilia Register.

7.2.5 Clinical Outcomes of Interest

The Roctavian and SoC Cohorts in this study will be compared regarding the clinical outcomes of bleeds, use of hemostatic treatments, and assessments of joint health, quality of life and pain. See Section 10.3 and the SAP for further detail on the planned comparisons. These clinical outcomes will be derived from data entered in the DHR at or after the index date during the follow-up period.

7.2.5.1 Bleeding events

The primary endpoint, as well as endpoints for secondary objectives regarding bleeding events, will be based on bleeding events recorded in the DHR. Categories of bleeding events, along with relevant variables collected in the DHR, are described in Table 6. Bleeding events will be compared regarding both annualized bleeding rates (ABRs), which allow for calculation based on variable amounts of time, and the proportion of participants with zero bleeds over a fixed period of time (eg, 1-year increments, among those with 2 years of follow-up, and/or among those with the full 3 years of follow-up for the AbD). Details on the calculation of these outcomes based on the bleeding events recorded in the DHR are described further in Section 10.3 and the SAP, including counting of events recorded on consecutive days. Bleeding events of a specific severity or occurring in a specific location (eg, a joint) are based upon the discretion of the physician recording the data in the DHR. PwSHA administered Roctavian will remain on prophylaxis for a time following the index date as endogenous FVIII production initiates, therefore the analytical follow-up period of bleeding events for the Roctavian Cohort will begin on 5 weeks post-infusion or 3 days after the end of routine FVIII prophylaxis (which ever occurs later), or 27 weeks after end of emicizumab prophylaxis consistent with analyses of the Roctavian clinical trials. The analytical follow-up period of the SoC Cohort will begin on the index date.

Table 6: Bleeding Events

Variable	Description	Currently captured in DHR	Time period for Analysis	Entry into DHR	Operational notes including Relevant Data Fields in DHR
Treated Bleeds	Bleeding events requiring treatment with FVIII	✓	Follow-up	Ongoing	Derived based on therapy usage recorded in the DHR for suspected, spontaneous, or unknown cause of bleeding (regardless of severity).
Major bleeds	Severe or life-threatening bleeds	✓	Follow-up	Ongoing	Treated bleeds (see above), but with severity recorded as ‘severe’ or ‘life-threatening’ in the DHR. Major bleeds will be a sub-set of treated bleeds.

Variable	Description	Currently captured in DHR	Time period for Analysis	Entry into DHR	Operational notes including Relevant Data Fields in DHR
Life-threatening bleeds	Life-threatening bleeding events	✓	Follow-up	Ongoing	Treated bleeds (see above) with severity recorded as 'life-threatening' in the DHR. Life-threatening bleeds will be a sub-set of treated bleeds and major bleeds.
Joint bleeds	Bleeds occurring in a joint or target joint	✓	Follow-up	Ongoing	Treated bleeds (see above) regardless of severity, but with a location/localization of 'joint' or 'target joint' in the DHR. Major bleeds will be a sub-set of treated bleeds.

DHR, German Hemophilia Register; FVIII, Coagulation factor VIII

7.2.5.2 Use of hemostatic treatments

Endpoints for secondary objectives regarding hemostatic therapy usage will be based on therapeutic usage of FVIII and emicizumab recorded in the DHR. Key endpoints for comparing use of hemostatic therapy, along with relevant variables collected in the DHR, are described in Table 7. Use of any FVIII or emicizumab, the number of uses (stratified by prophylaxis vs on-demand/for bleed treatment), amount of FVIII consumed and number of infusions will be compared between cohorts. Endpoints will be compared based on the total follow-up, as well as specific periods of time (eg, during the 2nd or 3rd year of follow-up). Details on the calculation of these outcomes based on the therapeutic usage recorded in the DHR are described further in Section 10.3 and the SAP. PwSHA administered Roctavian will remain on prophylaxis for a time following the index date as endogenous FVIII production initiates, therefore the analytical follow-up period of hemostatic therapy usage for the Roctavian Cohort will begin on 5 weeks post-infusion or 3 days after the end of routine FVIII prophylaxis (which ever occurs later), or 27 weeks after the end of emicizumab prophylaxis consistent with analyses of the Roctavian clinical trials. The analytical follow-up period of the SoC Cohort will begin on the index date.

For the Roctavian Cohort only, the proportion of participants who return to prophylactic hemostatic therapy, along with the time to return to prophylaxis will be described for those in the cohort who ended prophylaxis post Roctavian administration.

Table 7: Hemostatic Treatment during Follow-up

Variable	Description	Currently captured in DHR	Time period for Analysis	Entry into DHR	Operational notes including Relevant Data Fields in DHR
Use of hemostatic treatments	Use of any hemostatic treatments	✓	Follow-up	Ongoing	Derived based on therapy usage recorded in the DHR for FVIII and/or Emicizumab.
FVIII Consumption	FVIII consumption during follow-up	✓	Follow-up	Ongoing	Derived based on reported FVIII consumption for each therapeutic use of FVIII, reported for different prophylaxis types (see Table 4). Will be described based on total FVIII utilized in international units (IUs), as well as IU/KG based on availability of weight data (see note in Table 3).
Infusion/Injection Rate	Number of infusions/injctions during follow-up	✓	Follow-up	Ongoing	Providing data allows, derived based on the therapy usage and frequency of use during individual usage periods recorded in the DHR for any reason. Data is expected to be able to allow for summaries of annualized infusion/injection rate (AIR).
Return to prophylaxis	*For Roctavian Cohort only* Use of continuous prophylaxis	✓	Follow-up	Ongoing	Derived based on the therapy usage recorded in the DHR. Participants reporting use of a therapy for 'prophylaxis' in consecutive months and utilizing above a threshold of hemostatic treatment during follow-up after ending prophylaxis post Roctavian administration. Specific details of the definition for return to prophylaxis will be described in the SAP and may be updated with definitions maintained in the SAP based on therapies available for hemostatic prophylaxis. Definition utilized in this study is relevant to the fields that the DHR collects and will be aligned as best as possible to other definitions utilized external to this study.

AIR, annualized infusion/injection rate; DHR, German Hemophilia Register; FVIII, Coagulation factor VIII; SAP, Statistical Analysis Plan.

7.2.5.3 Clinical outcome assessments

Endpoints for secondary objectives regarding joint health, quality of life, and pain will be based on validated standardized measurements. Specifically, joint health will be assessed over time based on the Hemophilia Joint Health Score (HJHS), quality of life will be assessed based on the Haemo-Quality of Life assessment (QoL-A) questionnaire, and pain will be assessed based on the Brief Pain Inventory-Short Form (BPI-SF). These measured are described in Sections 7.2.5.3.1, 7.2.5.3.2, and 7.2.5.3.3 respectively. The current data fields in the DHR (as of the drafting of this protocol) allow for the recording of scores associated with the HJHS, but there are no data fields currently configured for the entry of quality of life nor pain questionnaires. It is anticipated that additional fields will be added to the DHR to allow for the recording of data associated with the questionnaires described in Sections 7.2.5.3.2 and 7.2.5.3.3 by the time that this study begins enrolling participants. Analyses of these instruments are described further in Section 10.3 and the SAP. As these instruments standardize collection of data for areas that are monitored in routine clinical practice, the assessments are expected to follow routine clinical follow-up, which is typically on an annual basis for patients. Physicians participating in the AbD are expected to enter data for these instruments collected relative to the study index date (eg, around the index date, and approximately annually for 3 years relative to the index date).

7.2.5.3.1 Hemophilia Joint Health Score

The HJHS is a validated outcome tool developed for the assessment of joint health in people with hemophilia (Feldman 2011). The ordinal joint score assesses 9 items in 6 index joints. The HJHS measures joint health, in the domain of body structure and function (ie, impairment), of the joints most commonly affected by bleeding in hemophilia: the knees, ankles, and elbows. This physical examination assessment tool conducted by a healthcare provider is sensitive enough to pick up the subtle early signs of joint damage. It is appropriate for monitoring joint change over time or assessing efficacy of treatment regimens in children receiving both prophylactic and on-demand therapy.

7.2.5.3.2 Haemo-QoL-A Questionnaire

The Haemo-QoL-A questionnaire is a validated hemophilia-specific health-related quality of life questionnaire for adults (Rentz 2008), including for adults undergoing gene therapy (Quinn 2022). It consists of 41 questions covering 6 domains (Physical Functioning, Role Functioning, Worry, Consequences of Bleeding, Emotional Impact and Treatment Concerns). Items are answered by patients on a 6-point Likert-type scale, ranging from 0 (None of the time) to 5 (All of the time). Higher scores mean better health-related quality of life or less

impairment for a particular subscale. The Haemo-QoL-A has a recall period of the “past 4 weeks” (Quinn 2022).

7.2.5.3.3 Brief Pain Inventory-Short form Questionnaire

The BPI-SF is a validated and frequently used patient-reported questionnaire that assesses pain severity and the impact of pain on daily functions (ie, pain interference) (Cleeland 2009). The BPI-SF measures generic pain (ie, is not indication-specific) has been used and validated in hemophilia (Kempton 2017), (Srivastava 2020), (Chantrain 2023).

Four questions measure pain intensity (worst pain, least pain, average pain, and pain now). The pain intensity items use an 11-point numerical scale with zero signifying ("no pain") and 10 signifying ("pain as bad as you can imagine"). The pain interference scale assesses the degree to which pain interferes with 7 constructs (General activity, Mood, Walking ability, Normal work, Relation with people, Sleep, and Enjoyment of life). The pain interference items use an 11-point numerical scale with zero signifying "does not interfere" and 10 signifying "completely interferes." Both the pain intensity and pain interference items have a recall period of the “last/past 24 hours”. Four other items allow patients to report on the nature of their pain.

7.2.5.4 Safety outcomes

Safety events of interest (hemophilia-related death, adverse events leading to hospitalization and death, and targeted adverse events of development of FVIII inhibitors, thromboembolic events, new malignant neoplasms) will be described for each cohort based on data recorded in the DHR. Categories of safety events where at least 10 events occur during the follow-up period in both study arms will also be compared between the Roctavian and SoC Cohorts in this study. The current data fields in the DHR (as of the drafting of this protocol) allow for the recording of some of the safety events of interest for the AbD, though it is anticipated that additional fields will be added to the DHR to allow for the recording of all safety events of interest. See Table 8 for detail on events currently captured and relevant data field when applicable. Safety events will be described and compared (when applicable) based on events recorded on the index date and/or during the follow-up period of each patient.

Refer to Section 9 for additional information on safety reporting expectations.

Table 8: Safety Events of Interest

Variable	Description	Currently captured in DHR	Time period for Analysis	Entry into DHR	Operational notes including Relevant Data Fields in DHR
Hemophilia-related death	Deaths occurring due to the disease	✓	Follow-up (inclusive of index)	Ongoing	Derived based information entered into the DHR when a participant is no longer enrolled in the DHR due to the reason being death and cause of death identified as hemophilia-related.
Adverse events leading to hospitalization and/or death	FVIII consumption during follow-up	X	Follow-up (inclusive of index)	Ongoing	The DHR captures information on medically relevant events including allergic reactions, thromboembolic events, thrombotic microangiopathy, and other with a free text field to specify the other category. For each event, the connection to hemophilia treatment (yes/no/unknown) is also recorded. It is currently (as of the drafting of this protocol) not possible to identify if an event led to hospitalization and/or death. It is anticipated that a field will be added to the DHR to specify if the event that led to hospitalization and/or death. Based on the anticipated additional field, those events that are related to hemophilia treatment and lead to hospitalization and/or death will be utilized for analyses.
Targeted Adverse Events					
Development of FVIII inhibitors	Positive inhibitor test(s) or requirement for ITT	✓	Follow-up (inclusive of index)	Ongoing	Based on recording of the DHR variables for positive inhibitor tests after enrollment in the DHR, or use of immune tolerant therapy (ITT). See Table 4 and SAP for additional information on definition for positive inhibitors based on 2 positive tests or 1 test and use of ITT.
Thromboembolic events	Occurrence of a thrombo-embolic event related to treatment	✓	Follow-up (inclusive of index)	Ongoing	Derived based recording of medically relevant event of thromboembolic event that has been identified as connected to hemophilia treatment. Occurrence of thromboembolic events regardless of relationship to treatment will also be described, but not compared.

Variable	Description	Currently captured in DHR	Time period for Analysis	Entry into DHR	Operational notes including Relevant Data Fields in DHR
New Malignancies	Occurrence of a malignancy	X (see operational note)	Follow-up (inclusive of index)	Ongoing	Occurrence of malignancies may be recorded based on the current medically relevant event fields captured in the DHR under 'other', though it is not possible to know differences in recording practices between sites. It is anticipated that the medically relevant event fields in the DHR will be updated to include additional events including new malignancy. Based on this update, events will be derived similar to thromboembolic events above, though a criteria of treatment related will not be applied.
Severe liver disease (liver failure or cirrhosis)	Occurrence of new severe liver disease	X	Follow-up (inclusive of index)	Ongoing	Occurrence of severe liver disease (liver failure or cirrhosis) may be recorded based on the current medically relevant event fields captured in the DHR under 'other', though it is not possible to know differences in recording practices between sites. It is anticipated that the medically relevant event fields in the DHR will be updated to include additional events including severe liver disease (defined as liver failure or cirrhosis). Based on this update, events will be derived similar to thromboembolic events above.

DHR, German Hemophilia Register; FVIII, Coagulation factor VIII; ITT, Immune tolerant therapy; SAP, Statistical Analysis Plan.

8 REMOVAL OF PARTICIPANTS AND STUDY TERMINATION

8.1 Participant Withdrawal from the Study

Participant (or their legally authorized representative) may withdraw their consent to participate in the study at any time without prejudice. The physician must withdraw from the study any subject who requests to be withdrawn. A subject's participation in the study may be discontinued at any time at the discretion of the physician and in accordance with his/her clinical judgment. Withdrawal from this study relates only to this study (and therefore the AbD) and does not impact follow-up of a participant in the DHR per local regulations.

Reasons for removal of a subject from the study include, but are not limited to, the following:

- Death
- Lost to follow-up
- Use of any investigational product or investigational medical device during the study
- Subject was erroneously admitted into the study or does not meet entry criteria per Section 5.2.1

The physician or designee must explain to each subject, before enrollment into the study, that for the evaluation of study results, the subject's protected health information obtained during the study will be shared with the sponsor, regulatory agencies, and the IRB/IEC/REB. It is the investigator's (or designee's) responsibility to obtain written permission to use protected health information per country-specific regulations, from each participant, or if appropriate, the subject's legally authorized representative. If permission to use protected health information is withdrawn, it is the investigator's responsibility to obtain a written request, to ensure that no further data will be collected from the subject and the subject will be removed from the study.

8.2 Lost to Follow-Up

It is not anticipated that participants will be lost to follow-up due to the routine clinical management of PwSHA, as well as data being collected consistent with ongoing disease management practices. However, a participant may be considered lost to follow-up if he repeatedly fails to attend visits at the site or respond to attempts at contact by the site. A participant will be deemed lost to follow-up at the discretion of the participants treating physician, as participants are expected to be seen consistent with routine clinical management. As PwSHA are expected to be seen at an HTC at least annually (and likely every 6 months), a participant may be considered lost to follow-up if he has not been seen, or no data has been reported into the DHR (whichever is later) for 18 months. Before a

participant is deemed lost to follow-up, the treating physician or designee should make every effort to regain contact with the participant.

For the purposes of analyses, a participant's follow-up will be censored at the end date of the most recent data entry period into the DHR. At the time of final data cut, any participant without data entered into the DHR over the full follow-up period of this AbD (index date + 3 years) will be considered lost to follow-up and similarly censored. In reporting participants lost to follow-up, participants deemed lost to follow-up at the discretion of the investigator will be reported separate from those considered lost to follow-up at the time of the final data cut.

8.3 Replacement of Participants

All subjects consenting to the AbD data collection during the identification period (see Section 5.1) will be included in the study. Participants will not be replaced if lost to follow-up or withdrawn from the study as a replacement participant would not be followed for 3 years by the time that the AbD is due to complete (AM-RL 2023).

8.4 Study Termination

BioMarin (the sponsor) reserves the right to discontinue the study at any time. Premature termination of the study may occur because of a regulatory authority decision, a change in the opinion of the IRB/IEC/REB, clinical or safety reasons, or at the discretion of the sponsor. The sponsor reserves the right to discontinue participation by an individual investigator or site for poor enrollment or noncompliance. Any decision to terminate the study will be promptly communicated to Investigators, regulatory authorities, and the IRB/IEC/REB. The investigator is responsible for communicating any decision to terminate the study to hospital staff involved in the conduct of the study and the participating subjects (and/or their legally authorized representative).

8.4.1 Futility Assessment

A futility analysis will be conducted at the 6-month and 18-month interim analyses to assess whether the study should be terminated early due to the inability to meet the required sample size for comparative analyses. The futility analysis will examine the total number of patients enrolled in the study, the number of patients in each of the SoC and Roctavian cohorts at the time, the amount of time remaining in the patient selection window, and the numbers of variables available for analysis. Assessments of potential futility and implications on study interpretation will be discussed in the reports associated with these interim analyses. Continued conduct of the study based on the futility assessment at these timepoints will be discussed with the G-BA.

A futility analysis will also be included as part of the 36-month and 54-month interim analyses to determine the observed ABR of each cohort. Implications on study interpretation will be discussed in the reports associated with these interim analyses. Continued conduct of the study based on the futility assessment at these timepoints will be discussed with the G-BA.

9 SAFETY DATA COLLECTION, RECORDING AND REPORTING

Secondary use of data in observational research means that there is no potential to collect individual serious and non-serious adverse events (AEs), pregnancy exposures, or incidents related to BioMarin products during the conduct of this research as the minimum criteria needed to report AEs, pregnancy exposures, and incidents are not present in the data source.

Therefore, the reporting of adverse drug reactions (ADRs) in the form of individual case safety reports will not be performed for data extracted from the DHR (GVP VI.C.1.2.1.b). It is assumed that reporting of corresponding safety data extracted/analyzed as part of this study has been appropriately performed in accordance with local requirements and documented at the time these data were collected through primary data collection mechanisms. On-site monitoring study monitoring visits (see Section 11.8) will be utilized to ensure that relevant AEs are reported are reported to the study sponsor for participants in this study consistent with local practice.

9.1 Local Requirement for Reporting of Safety Events

In Germany, physicians are obliged to report unintended drug reactions (unerwünschte Arzneimittelwirkungen) coming to their attention in the context of their therapeutic activity to the Drug Commission of the German Medical Profession (Arzneimittelkommission der deutschen Ärzteschaft, specialist committee of the German Medical Association) and incidents relating to the use of medical devices to the relevant competent authority (Model Professional Code for Physicians in Germany - MBO-Ä, 1997).

9.2 BioMarin Pharmacovigilance Contact Information

Contact information for BioMarin Pharmacovigilance is as follows:

BioMarin Pharmaceutical Inc.

Address:	105 Digital Drive Novato, CA 94949
Phone:	(415) 506-6179
Fax:	(415) 532-3144
Email:	drugsafety@bmrn.com

10 STATISTICAL CONSIDERATIONS

10.1 Sample Size Determination

The primary goal of hemophilia treatment is to reduce the bleeding rate or to achieve freedom from bleeding. As an approximation of the appropriate number of cases for the data collection accompanying the application, G-BA proposed 3 possible scenarios based on the endpoints freedom from bleeding and annual bleeding rate (ABR) which are assumed as a result of an orienting case number estimate:

1. Assuming a distribution of 1:5 between intervention and comparison group, 87.5% responders (defined as with freedom from bleeding) under the intervention and 35% responders under the comparison therapy under a shifted null hypothesis of RR = 2.0: 516 patients (intervention group n = 86, comparison group n = 430)
2. Assumption of a distribution of 1:5 between intervention and comparison group, 80.5% responders (with freedom from bleeding) under the intervention and 35% responders under the comparison therapy under a shifted null hypothesis of RR = 2.0: 1554 patients (intervention group n = 259, comparison group n = 1295)
3. Assumption of a distribution of 1:5 between intervention and comparison group, ABR = 0.85 (SD = 5.0) under the intervention and ABR = 3 (SD = 8.0) under the comparison therapy using a two-sample t-test method: 397 patients (intervention group n = 67, comparison group n = 330)

Although achieving freedom from bleeding is an important goal for treatment, utilizing this as the binary endpoint does not reflect the distribution of bleed outcomes. The distribution of bleed outcomes is better characterized based on a continuous measure, such as annualized bleeding rate, which can reflect both differences in patients with zero bleeds, as well as differences in bleeding rates for those who do experience bleeds. At the same time when applicable, using a continuous variable instead of using a binary variable derived from the same clinical outcome (eg, bleeding counts or ABR vs. freedom from bleeding) for statistical sample size evaluation and analysis will potentially increase the statistical power during the process.

Based on current estimates of patient enrollment, the study will be powered based on the ABR approach (approach # 3). Due to application of a shifted null hypothesis of RR = 2.0 for substantial effect size in the freedom from bleeding approach, expected patient numbers are expected to be insufficient to ensure adequate power. Therefore, we support and accept G-BA's ABR based approach for sample size justification, where the target sample size will be 397 patients in total with 1:5 between intervention and comparison group (Intervention group n = 67, comparison group n=330).

10.2 Populations for Analysis

All participants who consent to participate in this study and fulfill the inclusion/exclusion criteria (see Section 5.2) will be described, though the population analyzed may differ from the overall population as participants will be required to have complete data for variables included in the PS (eg, missing year of birth). The population may also be required to have data entered into the DHR covering at least the 12 months prior to index to confirm inclusion criteria, though all participants are expected to have at least 12 months of historic data based on the inclusion of adult PwSHA and relevant local reporting requirements into the DHR.

For specific analyses, the population included will be required to have data collected for the outcome of interest required for the analysis (eg, participants with a missing Haemo-QoL-A score at baseline would be excluded from an analysis of change from baseline in Haemo-QoL-A or a comparison of subjects achieving the MCID for the Haemo-QoL-A). A priori requirements for analyses are detailed further in the SAP, as for certain analyses the absence of an event (e.g., bleed events) are not considered missing. The population not included in an analysis due to missing data will be described if ≥10 participants in each study cohort are excluded. Additional requirements/exclusions for specific analyses based on observations in the data (notably after the initial data cut for the first interim analysis) will we documented in the SAP and described in reports.

The cohorts for comparison in this study include:

- **Roctavian cohort**: PwSHA without a history of or current inhibitors administered Roctavian during the study identification period.
- **SoC Cohort**: PwSHA without a history of or current inhibitors treated with FVIII replacement therapies or emicizumab and not administered Roctavian during the study identification period.

10.3 Statistical Analysis

The SAP will be finalized prior to the initial data cut to complete the 18-month interim analysis. A draft of the SAP including more technical and detailed description of the statistical analyses described in this Section has been completed in conjunction with this protocol. This Section is a summary of the planned statistical analyses of the most important endpoints, including primary and key secondary endpoints.

10.3.1 General Considerations

. Descriptive statistics include participant count, mean, median, standard deviation, minimum and maximum for continuous variables and count and percentage for categorical variables.

The 95% confidence interval for the mean and the percentiles may also be included, if appropriate. Hemostatic treatment variables will similarly be compared. Bleeding related variables will be analyzed and compared between Roctavian Cohort and SoC Cohort using appropriate statistical models including negative binomial model, logistic regression and other appropriate model. Safety variables will be summarized descriptively, unless at least 10 events occur for a specific variable during the follow-up period in both study arms.

10.3.2 Estimation of the Propensity Score

A PS is the probability of receiving treatment given an observed set of known covariates, which can be used to balance covariate values between the treated and control patients to obtain an unbiased estimate of treatment effect.

The PS in this analysis represents the probability of patients being in the Roctavian Cohort given the observed set of baseline patient characteristics. This will be calculated using a logistic regression model predicting treatment assignment from baseline characteristics.

PSs will be developed based on baseline characteristics of the study cohorts (see Section 10.2) described in Table 3 and Table 4. Potential variables for inclusion in the PS will be based upon variables identified from a literature review of factors associated with bleeding (specifically focused on literature from Germany), previous PS development for a comparison of Roctavian to FVIII prophylaxis based on studies that were part of the Roctavian clinical development (Liu, 2022; see appendix section 14.2 for further details), available data collected in the DHR, clinical input from health care practitioners (HCPs) in Germany managing PwSHA, and statistical relationships.

10.3.2.1 Variable identification based on previous work

Prior to the initial data cut for the interim analysis at 18 months after study initiation, a literature review will be conducted to identify potential variables for inclusion in the PS. The literature review will focus on data published from Germany describing the bleeding events among PwHA and PwSHA. Additionally, previous work to develop PS for a comparison of Roctavian to FVIII prophylaxis based on studies that were part of the Roctavian clinical development (Liu, 2022; see appendix section 14.2 for further details) will inform potential variables.

10.3.2.2 Variables collected in the DHR

Variables identified in the literature, as well as based on clinical input, will be compared to the variables currently collected in the DHR for consideration in the PS. Based on previous PS development work (Liu, 2022; see appendix section 14.2 for further details) it is expected

the DHR currently collects the key variables that would be included in a PS. These variables include: age, BMI, HTC/site, target joints, baseline ABR, baseline FVIII utilization and baseline prophylaxis type/class (SHL FVIII, EHL FVIII, PD FVIII, emicizumab).

10.3.2.3 Clinical input into PS

HCPs in Germany treating PwSHA with either Roctavian or SoC products will advise the study team regarding overall study conduct and interpretation, as well as inputting into variables identified for PS inclusion. HCPs are expected to provide input into variables both associated with the endpoint of bleeding events as well as factors associated with choosing Roctavian treatment.

10.3.2.4 Baseline comparison of groups for propensity score development

Patient characteristics will be presented for all baseline variables described in Table 3 and Table 4, along with tests for difference using appropriate statistical testing; Welch's t-test for continuous variables, and the Chi-square test for categorical variables.

Standardized mean difference (SMD) will be calculated for continuous and categorical variables. SMD represents the most commonly used statistic to examine the balance of covariate distribution between groups, with a value greater than 0.1 indicating imbalance between groups (Zhang 2019).

After propensity score methods have been applied, tabulations will be repeated with p-values and SMDs re-calculated to investigate any meaningful differences remaining after PS-adjustment, both in the characteristics included in the propensity scoring, and also those not included. Although all baseline characteristics will be presented for completeness, the balance of the variables included within the PS models will be the focus of interest due to the importance assigned to these characteristics.

In accordance with guidance that model-evaluation tools of the logistic regression are secondary to the balancing of participant characteristics (McMurry 2015), (Rubin 2004), sensitivity analyses will also be performed with the omission of highly correlated variables.

10.3.3 Application of the Propensity Score

Multiple PS adjustment methodologies will be considered for the primary analysis, with the specific method decided based on observations in the initial data cut for the interim analysis at 18 months after study initiation. Considering the intended sample sizes as well as the primary question of interest (eg, the benefit of Roctavian vs SoC), weighting methodologies will be preferred and *a priori* the primary analyses will utilize standardized mortality ratio weighting (SMRW). SMRW will better utilize all available data and weight the SoC Cohort

to the baseline characteristics of the Roctavian cohort, therefore maintaining the representativeness of the analysis to the PwSHA being administered Roctavian in Germany. Sensitivity analyses will be performed using alternative methods. Propensity score matching (PSM) is planned to be utilized as the main sensitivity method *a priori*, though other approaches may be considered. The approaches are further discussed in the SAP, including considerations when different methods would be applied. As the primary analysis plans to utilize SMRW and the *a priori* sensitivity analysis is planned to be PSM, these methods have been discussed below in Sections 10.3.3.1 and 10.3.3.2.

10.3.3.1 Standardized mortality ratio weighting

SMRW will be conducted to reweight the SoC Cohort to match the characteristics of the Roctavian cohort. To do this for the Roctavian cohort, the weight, W, assigned in the SMRW method for each individual *i*, based on PS, P_i, is:

$W_i = 1$

For the SoC Cohort, patients receive weights of:

$W_i = P_i / (1-P_i)$

The resulting analysis will have the SoC Cohort reweighted to match the Roctavian cohort.

10.3.3.2 Propensity score matching

PSM will be consider *a priori* for a sensitivity analysis and initially be performed using the procedure of 1:1 matching (alternative ratios will be explored based on the observed data), which matches each subject in the Roctavian Cohort with a participant in the SoC Cohort exhibiting the nearest PS (this is also known colloquially as 'greedy' matching) without replacement. If an appropriate match is not available, for example due to a lack of overlap in PS values between cohort, then cases (ie, participants in the Roctavian cohort) are discarded and the matched sample size for analysis is reduced accordingly.

Roctavian Cohort participants may be allowed to match with multiple SoC Cohort participants if alternative matching ratios are considered (eg, 1:2, 1:3, or 1:4). For the PSM, a caliper width of 0.2 times the standard deviation of the propensity score will be used (Austin 2011) and 'random' order.

10.3.4 Primary Objective

Objective: To compare the annualized bleeding rate for treated bleeds.

ABRs for treated bleeding events (see Table 6) will be compared between the Roctavian and SoC Cohorts after PS adjustment. *A priori* the PS adjustment is planned to be implemented

via SMRW, though an alternatives adjustment methodology may be utilized based on observations of the data. All participants with the variables recorded to derive the PS will be included in the analysis. Participants with no bleeds reported but data entered into the DHR will have an ABR of zero (ie, data is not considered missing).

ABRs will be compared over the full follow-up time for each patient in the study, as well as during annual increments during the follow-up. For analyses of annual increments, only those participants who have full follow-up for the time will be included in analyses. For example, analyses comparing ABRs during the first year will only include participants with ≥1 year of follow-up after the index date or analyses comparing ABRs through 2 years of follow-up will only include participants with ≥2 year of follow-up after the index date.

- Sample sizes are expected to be reduced in analyses of annual increments for interim analyses as data collection will be ongoing, and potentially reduce for final analyses due to censoring (see below).

Follow-up for ABRs will begin based on the dates below (as explained above in Section 7.2.5.1):

- Roctavian cohort: Whichever occurs latest- 5 weeks post-infusion or 3 days after the end of routine FVIII prophylaxis, or 27 weeks after last emicizumab prophylaxis injection.
    - Specific definition utilized for analysis may be refined for consistency with analyses of Roctavian clinical trials and to account for hemostatic therapies that become available during the course of the study. Any updates will be documented through the SAP and described in interim/final reports.
- SoC Cohort: Index date

Follow-up for ABRs will be censored for the analysis based the earliest date after index of withdrawal, loss to follow-up, enrollment of an interventional hemophilia clinical trial, death, end of reporting/follow-up period in the DHR, or end of study follow-up (eg, index date +3 years).

- For the Roctavian cohort**:** Participant returns to hemostatic prophylaxis. After return to hemostatic prophylaxis is identified (see Table 7) the date of the first administration of prophylactic therapy in the 3-month period will be utilized as the censoring date.
- For the SoC Cohort: Participants will additionally be censored if administered Roctavian or another HA GT (if available commercially).

ABRs will be calculated for each participant as the number of bleeds divided by the time between the start of follow-up and censoring event for the analysis, annualized to the number in 1 year. The mean of the individual participant ABRs for each cohort will be calculated and compared. The primary comparison of ABRs will be based on the absolute difference in the mean treated ABR between the Roctavian and SoC Cohorts utilizing a two-sample t-test (two sided).

10.3.5 Secondary Objectives

10.3.5.1 Objective: To compare the annualized bleeding rate for major, life threating, and joint bleeds.

ABRs for other bleeding outcomes described in Table 6 (major bleeds, life-threatening bleeds and joint bleeds) will also be compared between the Roctavian and SoC Cohorts after PS adjustment. The analysis approach will be consistent with the primary objective (see Section 10.3.4) regarding PS adjustment approach, analysis of the full follow-up time along with annual increments, start of bleed follow-up and censoring reasons, as well as measurement of treatment effect.

10.3.5.2 Objective: To compare the proportion of patients with zero bleeds for treated, major, life threating, and joint bleeds.

Proportion of patients with zero bleeding events for all bleeding outcomes described in Table 6 will be compared between the Roctavian and SoC Cohorts after PS adjustment, generally consistent with the analysis approach for ABRs (see Section 10.3.4 above) regarding PS adjustment approach, analysis of the full follow-up time along with annual increments, as well as, start of bleed follow-up and censoring reasons.

Differing from the approach for ABRs, analyses of the proportion of patients with zero bleeding will only include those participants with follow-up for the full time over which the proportion is calculated. For example, the overall analysis for the proportion of participants with zero bleeds for the full study period (ie, through 3 years of follow-up) will be those participants who were not censored. Additionally, the measurement of treatment effect for these analyses will be the absolute difference in the proportion of participants with zero bleeding events between Roctavian and SoC Cohorts utilizing a Chi-square test.

10.3.5.3 Objective: To compare the use of hemostatic medications.

The use of hemostatic medications will be compared between the Roctavian and SoC Cohorts after PS adjustment, generally consistent with the analysis approach for ABRs (see Section 10.3.4 above) regarding PS adjustment approach, analysis of the full follow-up time

along with annual increments, as well as start of follow-up and censoring reasons. Comparisons will be made regarding the variables in Table 7.

The proportion of patients utilizing any hemostatic treatments during follow-up will be described but will not be compared as 100% of the SoC Cohort will utilize hemostatic treatments. The proportion of patients utilizing any hemostatic treatments specifically for bleeds or short-term prophylaxis will be compared regarding the absolute difference in the proportion of participants utilizing a Chi-square test. Similar to the analyses of the proportion of patients with zero bleeding, only those participants with follow-up for the full time over which the proportion is calculated will be included in analyses.

The total FVIII per kg during follow-up will be compared between the cohorts. Total FVIII per kg for any reason will be compared based on the absolute difference in the mean total FVIII per kg between the Roctavian and SoC Cohorts utilizing a two-sample t-test (two sided). Similar to the analyses of the proportion of patients with zero bleeding, only those participants with follow-up for the full time over which the proportion is calculated will be included in analyses.

AIRs will also be compared between the cohorts. AIRs will be calculated for each participant as the number of infusions or injections divided by the time between the start of follow-up and censoring event for the analysis, annualized to the number of infusions/injections in 1 year. The mean of the individual participant AIRs for each cohort will be calculated and compared. The comparison of AIRs will be based on the absolute difference in the mean AIR between the Roctavian and SoC Cohorts utilizing a two-sample t-test (two sided).

10.3.5.4 Objective: To compare joint health, quality of life, and pain.

Descriptive statistics will be used to summarize the absolute and change from baseline at the time of assessment for the HJHS. A repeated measurement analysis model will be utlilzed to describe the overall trend in the HJHS over time. The mean change from baseline to final assessment approximately 3 years after index will be compared between the between the Roctavian and SoC Cohorts.

Descriptive statistics will be used to summarize the absolute and change from baseline at the time of an assessment for the total and domain scores for the Haemo-QoL-A and the BPI-SF. For the BPI-SF the pain interference and pain intensity scores will be taken as the domains. A repeated measurement analysis model will be used to compare the changes in scores between the treatment groups. Patients with an evaluable baseline score and at least one evaluable post-baseline score will be required for the specific analysis be included in the change from baseline analyses.

In addition, responder analyses will be considered for improvement and deterioration for the BPI-SF pain interference and pain intensity scales. The BPI-SF pain intensity score will be defined as the Question 5 “average pain”. The BPI-SF pain interference score will be defined as the average to all 7 subitems of Question 9 (9A to 9G).

All analysis details and scoring methods will be described in the SAP. It is expected that no missing data will be imputed.

All PROs comparisons will be interpreted after 3 years of follow-up, or latest available follow-up score if a full 3 years of follow-up is not available.

10.3.5.5 Objective: To compare safety events of interest.

Safety events outlines in Table 8 will be described in each cohort. Summary of the proportion, event rate, and incidence rate of each of the safety events among all participants by cohort. Safety events will be described from index through follow-up. Follow-up for safety events will be censored for the analysis based the earliest date after index of withdrawal, loss to follow-up, enrollment of an interventional hemophilia clinical trial, death (inclusive of date of death), end of reporting/follow-up period in the DHR, or end of study follow-up (eg, index date +3 years). Participants will similarly be censored analytically, as done in the primary analysis when returning to prophylaxis for the Roctavian Cohort or administration of Roctavian in the SoC Cohort, though additional descriptive analysis of safety events for these groups after the censoring event will conducted. All participants will be included in analyses of event and incidence rates, while analyses of the proportion of patients will only include those participants with follow-up for the full time over which the proportion is calculated.

Categories of safety events where at least 10 events occur during the follow-up period in both study arms will also be compared between the Roctavian and SoC Cohorts in this study.

10.3.5.6 Objective: To describe time to resumption of prophylactic treatment among patients administered Roctavian

Time between Roctavian administration (index date) and resumption of hemostatic prophylaxis (defined in in Table 7) will be described for the Roctavian Cohort only. The proportion who return to prophylaxis and time to resumption will be described among those in the cohort who ended prophylaxis post Roctavian administration. Summary statistics will be utilized to describe time to resumption including mean (SD), median (inter quartile range), minimum and maximum.

10.3.6 Other Analyses

Per the resolution requiring the Routine Data Collection and Evaluations for Valoctocogene Roxaparvovec (AM-RL 2023), additional analyses comparing outcomes between the Roctavian cohort and classes of SoC prophylaxis (e.g., SHL/PD FVIII, EHL FVIII, and emicizumab), as well as for the SoC cohort that is AAV 5 antibody negative will be evaluated. (Note that PwSHA treated with Roctavian will be AAV5 negative per the indication for use in Europe.)

The feasibility of conducting comparative analyses will be described during the 18-month interim report. As the therapeutic treatment strategy for an individual who consents to this study is made independently of the decision to participate in the study, the sample size of specific sub-cohorts by SoC therapeutic classes is not known. The feasibility of conducting a comparative analysis will be based on the observed characteristics of the sub-cohort, which will impact the ability of the PS to address confounding, as well as sample size (e.g., a sample size of 50 patients in a sub-cohort is the anticipated threshold for a comparison as 50 patients would yield approximately equal size cohorts with the planned Roctavian cohort). Similarly, the use of AAV antibody testing among PwSHA who are not considering gene therapy is not known currently. AAV antibody status is not known to impact clinical outcomes among PwHA and therefore is not part of routine clinical practice currently. The feasibility of a comparison to AAV 5 negative among those in the SoC cohort will be evaluated similarly to the SoC therapeutic classes (based on both observed characteristics and sample size). Feasibility of analyses will also consider the ability to conduct comparisons for all vs specific objectives (e.g., it may be possible to conduct sensitivity analyses for the primary objective, but not for secondary objectives due to missing data).

In addition to the evaluation of the pre-specified sensitivity analysis regarding SoC therapeutic classes and AAV 5 antibody status, other sensitivity analyses may be considered based on the observed characteristics of the cohorts that consent into the AbD. As the characteristics of the PwSHA in Germany who will receive Roctavian are not know, nor the characteristics of those on SoC therapies who will consent into the AbD, any additional analyses (e.g., stratified by age, restrictions based on chronic viral infection) will be detailed in the SAP and discussed in the interim reports (described below).

10.4 Interim Analyses

Interim reports are planned at 6, 18, 36 and 54 months after initiation of this study.

The interim report at 6 months will describe study progress and patient numbers.

Full interim analyses of all endpoints are planned at 18-, 36- and 54-month reports. The data reflected in these interim analyses are expected to reflect data captured in the DHR through approximately 4 to 6 months prior to the interim analysis as the interim analysis points reflect submissions of interim reports. These interim analyses in the 18-, 36- and 54-month reports will focus on the primary analyses but will not conduct the sensitivity analyses discussed in section 10.3.6. The feasibility of sensitivity analyses, along with other sensitivity analyses that are planned, will be discussed in these reports.

The SAP further describes the planned interim analyses in greater detail.

10.5 Limitations of the Research Methods

Due to the observational nature of this study, results will represent a range of real-world practice in German, though results may be influenced by site heterogeneity (eg, clinic structure, site specific clinical practices). The analysis intends to utilize site as a component of the propensity score (and will consider an analysis by site if necessary). Due to the regulations governing the DHR, data extracts from the DHR cannot (at the time of drafting this protocol) provide specific site identification numbers. Based on discussions with the DHR, it is anticipated that although site identification numbers cannot be provided, that patients managed at the same site will be able to be identified. If it is ultimately not possible to identify patients at the same site, the analysis will be limited in controlling for differential clinical management practices (e.g., recommendations for specific FVIII prophylaxis regimens, use of FVIII for suspected bleeds that may be anthropic associated pain), as well as reporting/recording practices that may differ between sites.

As discussed in Section 10.3.6, the characteristics of the population that utilizes Roctavian in the real world is not currently know and similarly the SoC population that will consent to the AbD is also not known. It is expected that due to the resolution restricting authority to provide care to those providers who participate in the required data collection. (AM-RL 2023a) that the Roctavian cohort will be generalizable to the full population administered Roctavian in Germany. The generalizability of the SoC cohort and similarity of the cohort to Roctavian cohort may be impacted by selection bias. PS will be utilized to address differences between the cohorts, though the ability of the PS (along with additional adjustments/clustering if needed) to control for these differences cannot be assessed till after data collection begins. It is anticipated that the methods described in this protocol and accompanying SAP will control for potential confounding and allow for an unbiased comparison between the cohorts.

Although the methods described in this protocol and accompanying SAP are anticipated to be able to control for potential confounding (particularly for comparisons of clinical measures

such as bleeds), it is anticipated that some potential variables that could impact clinical measures, such as bleeds, and clinical outcomes assessments will not be captured in the DHR. In particular, individual lifestyle choices (e.g., participation in sports and physical activities) and personal experience with Hemophilia A (e.g., individual discernment between a joint bleed vs joint pain, effectiveness of previous treatments) are not feasible to capture in an observational registry. The capture of these individualized components of disease experience would be difficult to capture even in an interventional clinical trial setting. While residual FVIII activity has been identified to account for around 70% of a bleeding phenotype, the remaining 30% is potentially related to other unexplained individual variables (Mancuso, 2018). It is anticipated that this individualized patient experience is particularly relevant for patient centric measures, such as health related quality of life, joint function and pain. These measures would be most clinically meaningfully described based on intra-patient comparisons, which accounts for the individualized management of hemophilia symptoms, as well as previous experiences with an individual's disease that are not possible to capture in a registry. Although, intraindividual comparisons would better control for an individual's experience, the AbD requires comparisons across cohorts. Use of responder analyses, as well as the potential inclusion of target joints in the PS particularly for joint health, are anticipated to address some of potential confounding from variables that are not possible to collect in an observational registry.

The data utilized for this analysis will be collected in the DHR. The DHR has the advantage of being an existing system with which German physicians are familiar and should minimize site burden for additional data collection specific to the AbD, though the DHR is more similar to a secondary data source for the purposes of this analysis. Due to the anonymized nature of the DHR, the DHR will be treated as the source data for the purposes of source data verification (see section 11.8). Data fields in the DHR were reviewed in the design of this study and additional data fields were requested to be added as needed. Despite these considerations in the design of the study, the administration of the DHR is not controlled by the study sponsor and therefore the potential for missing data and/or implausible data values are possible. Data monitoring activities (described in Section 11.8) are anticipated to minimize missing data and implausible values in the final data set, though data for interim analyses may be more prone to potential missing/erroneous data. As missing/erroneous data are possible, the extent of missing data (or data excluded due to implausible values) will be quantified (when applicable). Imputation for missing data may be considered based on the patterns of missingness and effect of missing data on the interpretability of the results. Further detail regarding missing data procedures will be documented in the SAP.

11 REGULATORY AND ADMINISTRATIVE CONSIDERATIONS

11.1 Ethical Conduct of Study

This study will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines including good clinical practice, the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
- Principles of Good Pharmacovigilance Practice
- International Society for Pharmacoepidemiology Guideline for Good Pharmacoepidemiology (ISPE GPP)
- Applicable laws and regulations

11.2 Institutional Review Board/Independent Ethics Committee

The protocol, protocol amendments, informed consent form (ICF), summary of product characteristics (SmPC)/label, and other relevant documents (eg, advertisements) as applicable must be submitted to, reviewed and approved by the IRB/IEC/REB before the study is initiated.

Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study subjects.

The investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
- Notifying the IRB/IEC of Serious Adverse Events (SAEs) or other significant safety findings as required by IRB/IEC procedures
- Providing oversight of the conduct of the study at the site and adherence to requirements all applicable regulations

11.3 Financial Disclosure

Investigators and sub-investigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities.

11.4 Informed Consent Process

The investigator or designee will explain the nature of the study to the subject or his/her legally authorized representative and answer all questions regarding the study.

The investigator or his/her representative will explain the nature of the study to the subject or his/her legally authorized representative and answer all questions regarding the study.

Subjects must be informed that their participation is voluntary. Subjects or their legally authorized representative (as determined by the laws of the jurisdiction in which the study is being conducted) will be required to sign a statement of informed consent that meets the regulatory requirements of the country or region where the subject consents and the IRB/IEC or study center. If there is no applicable law addressing the issue of who may be a legally authorized representative, a legally authorized representative will be an individual recognized by institutional policy as acceptable for providing consent on behalf of the prospective subject to the subject's participation in the procedure(s) involved in the study.

The medical record must include a statement that written informed consent was obtained before any study specific procedures or data collection activities were initiated and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.

Subjects must be re-consented to the most current version of the ICF(s) during their participation in the study. Subjects who reach the age of majority in their country while the study is ongoing will be asked to provide their own written consent again upon reaching the legal age of majority.

A copy of the ICF(s) must be provided to the subject or the subject's legally authorized representative.

11.5 Data Management

All data for this study will be collected and stored in the electronic DHR. Study site personnel is responsible for patient data collection and data entry into the DHR.

Validation of patient data in the clinical database will be carried out via automated edit checks as well as manual checks raised by clinical research associates during on-site routine monitoring visits.

11.6 Retention of Study Documents

The investigator/ institution should retain all study records (questionnaires, databases and subject identifiers) for at least 15 years after the completion or discontinuation of the study.

Subject files and other source data must be kept for the maximum period of time permitted by the hospital, institution of private practice, but not less than 15 years.

These documents should be retained for a longer period, however, if required by the applicable regulatory requirements or by a BioMarin agreement. BioMarin must be notified and will assist with retention should investigator/institution be unable to continue maintenance of files for the full 15 years. It is the responsibility of BioMarin to inform the investigator/institution as to when these documents no longer need to be retained.

11.7 Data Protection

Measures will be taken to ensure the privacy of subject data, including the use of subject numbers in the DHR. A list linking subject identification numbers with subject names and other personal information will be kept in a secure place, separate from the subjects' medical records. BioMarin will follow all applicable regulations and guidelines in the relevant locality, country, and/or region to protect the privacy of subject data.

Subjects will be assigned a unique identifier by the DHR. Any subject records or datasets that are transferred to the sponsor will contain the identifier only; subject names or any information which would make the subject identifiable will not be transferred.

The subject must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the subject, who will be required to give consent for their data to be used as described in the informed consent.

The subject must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

In the event of a data security breach, participating institutions, study vendors, and/or BioMarin will take appropriate action according to their local processes and report to appropriate regulatory agency(ies) according to applicable laws and regulations.

11.8 Study Monitoring

Sites will be managed and monitored throughout the duration of the study according to the approved Study Monitoring Plan. Trained and qualified personnel from the sponsor or a designee will oversee site participation and data quality by means of both remote site management, data review and on-site visits. To minimize the potential for bias in the use of registry data, on-site visits may involve source data verification between the data set received by BioMarin from the DHR, against entries made into the DHR (source data). It is

anticipated that 100% source data verification will be performed on inclusion and exclusion criteria and primary endpoint data fields and further data fields for source data verification. Further details will be outlined in the Study Monitoring Plan.

It is anticipated that at least 2 routine monitoring on-site visits per annum, per site will be performed. The first routine monitoring visit will be performed within 4 weeks of inclusion of the first patient at each study site and further on-site visits will be dependent on the enrollment rate and data quality, at each participating site. This will be further outlined in the Study Monitoring Plan for the study.

12 PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

The posting of study information and study results will comply with applicable national regulatory requirements and BioMarin's data sharing policy available at https://www.biomarin.com/data-request-form/.

13 REFERENCES

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14 APPENDICES

14.1 Appendix 1 - Protocol Amendment History

None

14.2 Appendix 2 – Selected Sections of Study 270-804 including PS score development

14.3 Appendix 3 – DHR Data Collection Fields (German)

14.4 Appendix 4 – DHR Data Collection Fields (English Translation)

BioMarin

Comparative Effectiveness of Roctavian to Standard of Care Hemostatic Therapies in Germany Among People with Severe Hemophilia A – A Prospective Non-Interventional Study Utilizing Data Collected in the German Hemophilia Register

Statistical Analysis Plan (SAP)

Date: June 29, 2023, Original

Prepared For:

[redacted]

BioMarin Pharmaceutical, Inc.
San Rafael, CA 94901

Prepared By:

[redacted]

SAP Approval and Sign-off

I confirm that I have read the contents of this SAP and its attachments. I approve the SAP in its current form.

BioMarin

Print name and title here	Signature	Date

[redacted] **Principal**

Print name and title here	Signature	Date

[redacted] **Statistician**

Print name and title here	Signature	Date

[redacted] **Author *(if different from the Statistician*)**

Print name and title here	Signature	Date

List of Tables

List of Figures

1. Table of Contents

2. List of Abbreviations

Abbreviation	Definition
AAV5	Adeno-associated virus type 5
AbD	Anwendungsbegleitende Datenerhebung
ABR	Annualized bleeding rate
ADR	Adverse drug reaction
AE	Adverse event
AIC	Akaike information criterion
AIR	Annualized infusion/injection rate
ATE	Average treatment effect
BMI	Body mass index
BPI-sf	Brief Pain Inventory – short form
BU	Bethesda unit
CI	Confidence interval
Cm	Centimeter
COA	Clinical outcome assessment
DHR	Deutsches Hämophilieregister
dL	Deciliter
eCRF	Electronic case report form
ED	Exposure day
EHL	Extended half-life
EMA	European Medicines Agency
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
FVIII	Coagulation factor VIII
G-BA	Gemeinsamer Bundesausschuss (translated to Federal Joint Committee)
GEE	Generalized estimation equation
GLM	Generalized Linear Model
GPP	Good Pharmacoepidemiology Practices
GVP	Good Pharmacovigilance Practices
HA	Hemophilia A
HCV	Hepatitis C virus
HJHS	Hemophilia Joint Health Score
HR	Hazard ratio
HTC	Hemophilia treatment center
IEC	Independent ethics committee
IPTW	Inverse probability of treatment weighting
IQR	Interquartile range
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (translated to Institute for Quality and Efficiency in Health Care)
IRB	Institutional Review Board
ITT	Immune tolerant therapy
IU	International Units
Kg	Kilogram
LTPS	Logit transformed propensity score
MCID	Minimal clinically important differences
mg	Milligram
ml	Milliliter
OR	Odds ratio
PD	Plasma-derived
PJ	Problem joints
PSM	Propensity score matching

PwSHA	People with severe hemophilia A
QC	Quality control
QoL	Quality of life
RR	Risk ratio
SAP	Statistical analysis plan
SD	Standard deviation
SHL	Standard half-life
SMD	Standardized mean difference
SMRW	Standardized mortality ratio weighting
SoC	Standard of care
US	United States
vg	Vector genomes
VIF	Variance inflation factor

3. Abstract

<table>
<tr><th>Protocol Number</th><th colspan="2">270-603</th></tr>
<tr><td>Title of Study</td><td colspan="2">Comparative Effectiveness of Roctavian to Standard of Care Hemostatic Therapies in Germany Among People with Severe Hemophilia A. A Prospective Non-Interventional Study Utilizing Data Collected in the German Hemophilia Register.</td></tr>
<tr><td>Phase and Type of Study</td><td colspan="2">Phase IV non-interventional prospective study, to comparative the effectiveness of Roctavian to the Standard of Care (SoC) hemostatic prophylaxis therapies</td></tr>
<tr><td>Study Objectives and Endpoints</td><td colspan="2">The aim of this non-interventional study is to evaluate the overall effectiveness and safety of Roctavian compared to SoC hemostatic prophylaxis treatment for (PwSHA).
The study objectives and endpoints below will compare Roctavian and SoC prophylaxis treatments with coagulation factor VIII (FVIII) or emicizumab, unless otherwise noted.</td></tr>
<tr><td></td><th>Objectives</th><th>Endpoints</th></tr>
<tr><td></td><td>Primary:</td><td></td></tr>
<tr><td></td><td>• To compare the annualized bleeding rate for treated bleeds.</td><td>• Bleeding events requiring treatment with exogenous coagulation factor VIII (FVIII).</td></tr>
<tr><td></td><td>Secondary:</td><td></td></tr>
<tr><td></td><td>• To compare the annualized bleeding rate for major, life threating, and joint bleeds.</td><td>• Major bleeding events.
• Life-threatening bleeding events.
• Bleeding events occurring in the joint.</td></tr>
<tr><td></td><td>• To compare the proportion of patients with zero bleeds for treated, major, life threating, and joint bleeds.</td><td>• Bleeding events requiring treatment with exogenous FVIII.
• Major bleeding events.
• Life-threatening bleeding events.
• Bleeding events occurring in the joint.</td></tr>
<tr><td></td><td>• To compare the use of hemostatic medications.</td><td>• Prophylactic hemostatic treatments.
• On-demand hemostatic treatments.</td></tr>
<tr><td></td><td>• To compare joint health, quality of life, and pain.</td><td>• Hemophilia joint health score (HJHS).
• Haemo-Quality of Life assessment (QoL-A).
• Brief Pain Inventory-Short Form (BPI-SF).</td></tr>
<tr><td></td><td>• To compare safety events of interest.</td><td>• All cause death.
• Hemophilia-related death.
• Adverse events leading to hospitalization or death.
• Targeted adverse events of development of FVIII inhibitors, thromboembolic events, new malignant neoplasms, and severe liver disease (liver failure or cirrhosis).</td></tr>
<tr><td></td><td>• To describe time to resumption of prophylactic treatment</td><td>• Resumption of prophylactic hemostatic treatments.</td></tr>
</table>

	among patients administered Roctavian.	
Study Duration	Q1 2024 to Q3 2028	
Study Population	Adult PwSHA and without a history of (or current) inhibitors to FVIII in Germany.	
Sample Size	Approximately 70 PwSHA in the Roctavian cohort and approximately 330 PwSHA in the SoC cohorts.	
Medicinal Products	Roctavian. Hemostatic prophylaxis treatments; FVIII replacement therapies or emicizumab.	
Summary of Eligibility Criteria	Adult (≥18 years old) male PwSHAs registered in the German Hemophilia Register (DHR) database previously administered Roctavian or hemostatic prophylaxis with FVIII or emicizumab during the study identification period with no history of (or current) FVIII inhibitor.	

Data Elements of Interest	Key data elements to compare or describe outcomes in the Roctavian and SoC Cohorts include:
	• Bleeding Events
	• SoC Hemostatic Treatment Usage
	• Clinical Outcome Assessment Tools
	  ○ Hemophilia Quality of Life assessment (Haemo-QoL-A)
	  ○ Hemophilia Joint Health Score (HJHS)
	  ○ Brief Pain Inventory-Short Form (BPI-SF)
	• Safety Events	

Statistical Analysis	Comparison of outcomes between the Roctavian and SoC cohorts after propensity score adjustment for differences in baseline characteristics (e.g., demographic and clinical variables recorded in the DHR prior to the index date).	

4. Amendments and Updates

There may be occasions where slight changes may be required. Minor changes can be accommodated and if isolated may be undertaken with no change to budget.

Major Amendments	Minor Amendments
• ….. • ….. • …..	• …… • …… • ……

In the event that there are a significant number of changes or substantial work effort is required to accommodate (changes necessitating greater volumes of results or further programming) [redacted] would likely submit a change order or an equivalent document. Prior discussion would always occur between project leads before and changes would be made.

Number	Date	Section of the SAP	Amendment or update	Reason

5. Rationale and Background

Hemophilia A (HA) is an X-linked recessive bleeding disorder that affects approximately 1 in 5,000 males.[1, 2] It is caused by mutations in the factor VIII (FVIII) gene that codes for FVIII protein, an essential cofactor in the coagulation pathway. Severe HA is classified as FVIII activity less than 1% of wild-type (< 1 international units/deciliter [IU/dL]), moderate disease comprises 1-5% of wild-type activity and the mild form is 5-40% activity. The clinical manifestations of severe HA such as spontaneous bleeding episodes, predominantly in joints and soft tissues, with a substantially increased risk of death from hemorrhage when the brain is involved remain frequent. Bleeding into joints can cause acute pain and swelling and can result in reduced range of joint motion, long-term cartilage damage and debilitating hemophilic arthropathy.[3, 4] Early use of prophylaxis is recommended following diagnosis of HA to maintain joint health and prevent joint destruction.[5, 6] However, despite the use of prophylaxis many patients still experience joint bleeds, which may lead to joint deterioration over time.[7]

Prophylaxis also poses a substantial treatment burden on the individual patients.[8] Most patients in Germany use FVIII substitution in their prophylactic regimen with 2-3 intravenous injections per week. As of March 2019, people with severe HA (PwSHA) can use prophylaxis with a bispecific antibody one per week to once every four weeks, although FVIII or bypass drug treatment is also required for hemorrhages that occur during this therapy.[9]

Valoctocogene roxaparvovec (ROCTAVIAN®) is a gene therapy medicinal product that expresses the B-domain deleted SQ form of FVIII and is delivered by a one-time intravenous infusion. It was approved by the European Commission on 24 August 2022 for the following indication: treatment of severe HA (congenital FVIII deficiency) in adult patients without a history of FVIII inhibitors and without detectable antibodies to adeno-associated virus serotype 5 (AAV5).

This study is being conducted to fulfil the Federal Joint Committee (G-BA; Gemeinsamer Bundesausschuss) requirement(s) for the Anwendungsbegleitende Datenerhebung (AbD; observational data collection) to support Roctavian approval in Germany. Specifically, this study will provide data on the comparative effectiveness of Roctavian to standard of care (SoC) hemostatic prophylaxis treatments among PwSHA without a history of FVIII inhibitors. Safety will also be described (and compared, if warranted) among these populations to understand potential differences.

6. Research Questions and Objectives

The aim of this study is to evaluate the overall effectiveness and safety of Roctavian compared to SoC hemostatic prophylaxis treatments for PwSHA. Primary and secondary objectives are outlined in Table 1.

The specific objectives are listed below. All objectives will compare Roctavian and SoC with FVIII or emicizumab, unless otherwise noted.

Table 1: Objectives and Endpoints

Objectives	Endpoints
Primary	
• To compare the ABR for treated bleeds between Roctavian and SoC prophylaxis treatments including FVIII and emicizumab.	• Bleeding events requiring treatment with exogenous FVIII
Secondary	
• To compare the ABR for major, life threatening, and joint bleeds between Roctavian and SoC prophylaxis treatments including FVIII and emicizumab.	• Major bleeding events • Life-threatening bleeding events • Bleeding events occurring in the joint
• To compare the proportion of patients with zero bleeds for treated, major, life threatening, and joint bleeds between Roctavian and SoC prophylaxis treatments including FVIII and emicizumab.	• Bleeding events requiring treatment with exogenous FVIII • Major bleeding events • Life-threatening bleeding events • Bleeding events occurring in the joint
• To compare the use of hemostatic medications between Roctavian and SoC prophylaxis treatments including FVIII and emicizumab.	• Prophylactic hemostatic treatments • On-demand hemostatic treatments
• To compare joint health, QoL, and pain between Roctavian and SoC prophylaxis treatments including FVIII and emicizumab.	• HJHS • Haemo-QoL-A • BPI-sf
• To compare safety events of interest between Roctavian and SoC prophylaxis treatments including FVIII and emicizumab.	• All cause death • Hemophilia-related death • AEs leading to hospitalization and death • Targeted AEs of development of FVIII inhibitors, thromboembolic events, new malignant neoplasms, and severe liver disease (liver failure or cirrhosis)
• To describe time to resumption of prophylactic treatment among patients administered Roctavian.	• Time to resumption of prophylactic hemostatic treatments

Abbreviations: ABR: annualized bleeding rate; AE: adverse event; BPI-sf: Brief Pain Inventory-short form; FVIII: coagulation factor VIII; HJHS: Hemophilia Joint Health Score; QoL: quality of life; SoC: standard of care

7. Research Methods

7.1. Study Design

This non-interventional cohort study will enroll adult PwSHA treated in routine clinical practice with either Roctavian or SoC hemostatic prophylaxis treatment with FVIII replacement therapies or emicizumab in Germany. Study participants will be followed based on data prospectively entered into the German Hemophilia Register (DHR). All participants are expected to have previously enrolled in the DHR due to local regulations. Study participants will consent for their data that is collected in the DHR to be utilized for this study, consistent with the requirements of the AbD. Participants will provide consent during a study identification window beginning in Q1 2024 and ending in Q3 2025. This study identification window will allow for 3 years of follow-up for each participant in the DHR prior to the data cut required to report on the study for the purposes of the AbD (report due Q1 2029).

During the study identification window, participants will be assigned to a study cohort based on the treatment that was received during the identification window. All participants receiving Roctavian during the identification window will be assigned to the Roctavian Cohort. Participants receiving SoC hemostatic prophylaxis treatment only during the identification window will be assigned to the SoC Cohort. Index date will be defined as the date of Roctavian administration for PwSHA treated with Roctavian (Roctavian Cohort) and the date of consent for PwSHA treated with SoC products (SoC Cohort). Participants will be followed for 3 years after index date (follow-up period) based on data extracted from the DHR. If a participant in the SoC Cohort subsequently receives Roctavian during follow-up after the identification period, their data will be censored for analysis at the time of Roctavian administration. Study participants will be followed consistent with the Study Elements of Interest (see Study Protocol and Section 7.4). The study aims to enroll at least 70 PwSHA into the Roctavian Cohort and at least 330 PwSHA into the SoC Cohort. The study is anticipated to complete in Q3 2028. The study completion date is based on allowing time to analyze data and submit a report per the AbD defined deadline of February 2029. Changes to the AbD defined deadlines for the report would result in changes to the study completion timeframe, as well as the identification window described above.

The Roctavian and SoC Cohorts will be compared based on events observed during the follow-up period regarding bleeding events, use of hemostatic medication, clinical outcome assessments measuring joint health, quality of life, pain, and safety (hemophilia-related death, adverse events leading to hospitalization and death, and targeted adverse events of FVIII inhibitor development, thrombotic events, and new malignancies). PwSHA in Germany are generally seen at a Hemophilia Treatment Center every 6 months and therefore it is expected that clinical outcome assessments on joint health, quality of life and pain would be assessed at those timepoints.

Comparisons of safety will be conducted if warranted by the number of events observed. The occurrence of and time to resumption of prophylactic hemostatic therapy will also be described among the Roctavian Cohort during the follow-up period. The Roctavian and SoC Cohorts will be compared after propensity score adjustment for differences in baseline characteristics (e.g., demographic and clinical variables recorded in the DHR prior to the index date). These characteristics will also be used to describe the cohorts and to inform the propensity score. Exact variable included in the propensity score will be based on statistical, as well as clinical associations, between baseline characteristics and the likelihood of receiving the gene therapy. Variables included in the propensity score along with the propensity score adjustment method will be selected after the cohorts are described.

7.2. Study Estimand

Two estimands will be applied for this study – the treatment policy estimand and the hypothetical estimand. The treatment estimand ignores intercurrent events (so not applying censoring or any missing data analysis), while the hypothetical estimand may use censoring or missing data analysis methods to derive an estimate incorporating the effect of an intercurrent event like treatment switching. The treatment policy estimand can be overly conservative if switching occurs between the treatment arms in an analysis, while the hypothetical estimand is targeting to adjust for this effect. In the case of the 270-603 study design, along with the management and administration of gene therapy the treatment policy (similar to intent to treat analysis) would be overly conservative in the setting of this study. In particular, the administration of Roctavian will include continuation of SoC prophylaxis therapy in the initial weeks after infusion, possibility of patients in the Roctavian cohort to return to prophylaxis, and the potential for PwSHA in the SoC cohort to switch to Roctavian after the study identification window, cause the treatment policy estimand to be overly conservative for the primary objective of this study. Thus, the hypothetical estimand is the primary estimand, but the treatment policy estimand will be applied as necessary to check the robustness of the results and for outcomes where the hypothetical estimand is warranted (e.g. comparisons of safety).

7.3. Setting

7.3.1. Study Time Period

The study period from Q1, 2023, to Q3, 2028 represents the entirety of the dataset. The patient selection window will be between Q1, 2024, and Q3, 2025. The 12 months immediately prior to their index date will be utilized for baseline measurement of clinical variables such as bleeding events and hemostatic medication utilization. It is anticipated that all patients will have 12 months baseline data in the DHR prior to the index date. Availability of at least 12 months baseline data will be assessed in the observed data and is expected to be a requirement for the analytic dataset for comparison based on the variables anticipated to be included in the propensity score. Need for this requirement and/or considerations for not implementing this requirement will be discussed in the interim/final reports, as well as, documented as amendments in this SAP. Patients will be followed in the cohorts for three years from their index date.

The study completion date is based on allowing time to analyze data and submit a report per the AbD defined deadline of February 2029. Changes to the AbD defined deadlines for the report would result in changes to the study completion timeframe, as well as the identification window described above.

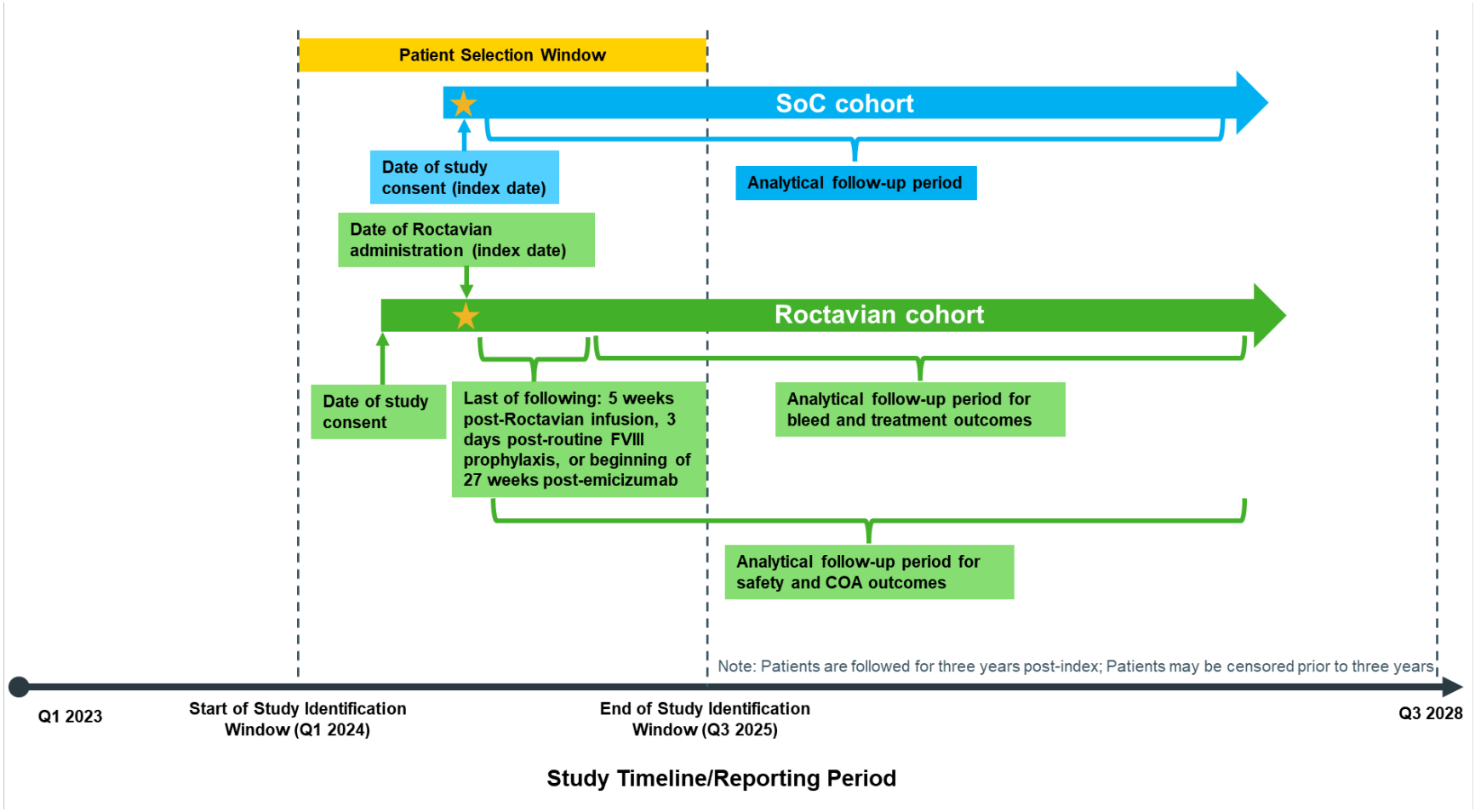

Figure 1. Study Timeline/Reporting Period

Abbreviations: COA: clinical outcome assessment; SoC: standard of care

7.3.2. Index Date

For patients in the Roctavian cohort, the index date will be the date of Roctavian administration during the selection window (Q1 2024, to Q3 2025). For patients in the SoC cohort, the index date will be the date of patient consent into the study during the same selection window. Alignment of index dates between Roctavian and SoC patients will be considered, and granularity of this alignment will be informed by study consent date data availability (e.g., month, quarter, or year).

7.3.3. Follow-up Period and Censoring

Patients will be followed for three years post-index date. Patients will be censored from the study due to any of the following reasons:

- Patient or their legally authorized representative withdraws their consent to participate in the study
- Death
- Lost to follow-up (repeatedly fails to attend visits or respond to attempts at contact)
- Use of any investigational product or investigational medical device during the study period
- For SoC cohort, if a patient is administered Roctavian after study consent

Follow-up time will end at the point at which any of the above events occur. For participants who withdraw from the study, initiate participation in a clinical trial, and/or initiate gene therapy (if in the SoC Cohort after the identification period), physicians are expected to enter data for the variables 'Data entered as observed after index' or 'End of Follow-up' with the data censored in the analysis at the date of withdrawal/trial initiation/gene therapy administration.

If patients are censored from the study while the selection window is ongoing, new patients may be selected for replacement.

7.3.4. Study Population

The study population will include male PwSHA without a history of inhibitors to FVIII in Germany. Patients will be identified from the DHR (see Section 7.5.1 for further description of the DHR) and are expected to provide written informed consent to be included in this study. Patients will be captured in either the Roctavian or SoC cohorts based on the treatment they receive during the study selection window of Q1, 2024, to Q3, 2025. The study aims to enroll at least 67 PwSHA into the Roctavian cohort and at least 330 PwSHA into the SoC cohort. The therapeutic treatment strategy for an individual who consents to this study is made independently of the decision to participate in the study and enrolment into this study will not inform the treatment strategy.

Patients will be selected into one of two mutually exclusive cohorts based on the treatment they receive for HA. The Roctavian cohort will include patients who received Roctavian during the selection window. The index date for these patients will be the date Roctavian is administered. The SoC cohort will include patients who received ≥1 prophylactic treatment with recombinant or human plasma-derived (PD) blood coagulation FVIII or emicizumab for ≥12 months prior to consenting to study participation. Patients in the SoC cohort cannot have a history of exposure to Roctavian.

7.3.5. Patient Selection

7.3.5.1. Inclusion Criteria

Patients will be included in the study if they meet all the following criteria:

- Male PwSHA as recorded in the DHR
- ≥18 years of age at index
- Treatment with Roctavian or SoC hemostatic prophylaxis
    - Participant administered commercially available Roctavian. Note: Assignment of a therapeutic strategy is not determined by this protocol.
        - OR
    - Has received prophylactic treatment with FVIII or emicizumab for at least 12 months prior to study entry.
- Participant (or their legally authorized representative, if appropriate) have provided written, signed informed consent to participate in this study
    - Note: those identified as participating in the AbD within the DHR are assumed to have provided consent. Actual consent documents will be held at the site and outside of the data extract that would be expected from the DHR.

7.3.5.2. Exclusion Criteria

Patients will be excluded from the study if they meet any of the following criteria:

- Is currently in, or previously participated (in the last 12 months before index), an interventional clinical trial involving an investigational product to treat HA
- History of inhibitors against FVIII ever (or current) as recorded in the DHR prior to index

7.3.5.3. Inclusion/Exclusion Criteria Variables

Table 2 outlines the variables and operational definitions of the inclusion/exclusion criteria. Variable definitions will be finalized based on data availability in the DHR during the data analysis phase.

Table 2: Inclusion/Exclusion Criteria Variables

Variable	Currently captured in DHR	DHR data field name	Operational definition/description
Clinical trial participation	Yes	• Participation in clinical trial (in the last 12 months before index) • Current participation in clinical trial • Name of the clinical trial	• No (exclude patient if yes) • Clinical trial name (free text field) to be utilized to specifically exclude interventional trials, if feasible; If not feasible, any clinical trial will be excluded • Participation in AbD and/or non-interventional studies of Roctavian will not result in exclusion • Further refinement to this variable may be required based on the observed data
History of Inhibitors (ever)	Yes	• Diagnosis • Inhibitor tests against FVIII/FIX	• Yes/No • Based on any recording of the DHR variables for inhibitors developed

Variable	Currently captured in DHR	DHR data field name	Operational definition/description
		positive in this reporting period • Occasion • Positive/negative result	before the patient started treatment at the current treatment center, positive inhibitor tests after enrollment in the DHR, or use of ITT • Exclusion will be based upon either 2 positive inhibitor tests (regardless of occurrence before or after enrollment in DHR) or 1 positive inhibitor tests (regardless of occurrence before or after enrollment in DHR) and use of ITT • Use of ITT will be identified if occasion = "ITT" • Titer (BU/ml) 0.0-1000.0 • Titer values (BU/ml) based on the test assay used will be assessed to validate a positive test (especially in the case of missing positive test results); a value <0.5 BU/ml will be used to identify presence of inhibitors
Severe HA	Yes	• Diagnosis • Hemophilia severity • Factor residual activity	• Severe (exclude patient if moderate, mild, or subclinical) • Confirm severe HA if FVIII antigen level <1%
Sex	Yes	• Gender	• Male (exclude patient if female or diverse)
Age	Yes (calculated)	• Month and year of birth	• Age at Index Date ≥18 years • If missing year of birth to calculate age at index, exclude patient
Treatment with prophylaxis inclusion	Yes	• Preparation/ medicinal product • Gene therapy	• Patients who are administered Roctavian or SoC medication as recorded in the DHR • For Roctavian cohort, gene therapy administration • For SoC cohort, patient has received prophylactic treatment with FVIII or emicizumab for at least 12 months prior to study entry • Index SoC drug listed for EDs >50 with date of treatment closest to (but not after) the index date; SoC drug must be listed in Table 4

Abbreviations: AbD: Anwendungsbegleitende Datenerhebung; BU/ml: Bethesda unit/milliliter; DHR: Deutsches Hämophilieregister; ED: exposure days; FVIII: coagulation factor VIII; FIX: coagulation factor IX; HA: hemophilia A; ITT: immune tolerant therapy; SoC: standard of care

Note: It is expected that variables that are not currently captured in the DHR or partially captured in the DHR will be fully captured at the time of the analysis.

7.4. Variables

The following sections outline all study variables to be used in this study from the DHR. For each variable, the DHR data field name as well as the operational definition and/or description of the variable is outlined. As a note, several variables from the DHR may be outlined to operationalize a variable for use in this study (e.g., dates, event, etc.). Variable definitions will be finalized based on data availability in the DHR during the data analysis phase.

7.4.1. Baseline Variables

Table 3 includes study variables that will be captured to describe the Roctavian and SoC cohorts based on data collected on or before their index date, or to be entered at the index date reflecting annual reporting into the DHR for the time period prior to the index date. As a note, all PwSHA are expected to have 12 months of data prior to their index date. Measures will be assessed at the most recent time point prior to the index date, unless otherwise specified.

Table 3: Baseline Variables

Variable	Currently captured in DHR	DHR data field name(s)	Operational definition/description
Unique patient ID	Yes (calculated)		• Calculated field based on a de-identified study center code and unique patient code (e.g., patient at study center A may be identified as A-101)
Index date	No		• ddmmyyyy • Date of Roctavian administration for Roctavian cohort • Date of study consent for SoC cohort
Age	Yes (calculated)	• Month and year of birth	• Age at Index Date (continuous) • Age groups: 18-40, 41-64, 65+ • Age groups in 5-year increments • Age groups may further be informed by the data
Age at HA diagnosis	Yes (calculated)	• Month and year of birth • Date of diagnosis	• Age at HA diagnosis derived from patient's month/year of birth and date of diagnosis, unless date of diagnosis is recorded as "unknown" • Reported similar to the Age variable above
Age at first FVIII administration	Yes (calculated)	• Month and year of birth • Date of the first factor administration	• Age at first FVIII administration derived from patient's month/year of birth and date of first FVIII administration, unless date of administration is recorded as "unknown"
HTC	Yes		• Derived from the site associated with study consent and primarily managing a participant • Deidentified form based on HTC identifier collected in DHR
Height (within 12 months	Yes	• Size	• Patient height (cm)

Variable	Currently captured in DHR	DHR data field name(s)	Operational definition/description
before index date)			
Weight (within 12 months before index date)	Yes	• Weight	• Patient weight (kg)

BMI (within 12 months before index date)	Yes (calculated)	• Weight; Size	• Calculated field from weight (kg) and height (cm) variables (kg/m^2)[10]
			  • <18.50 (underweight)
			  • 18.50 - <25.00 (normal range)
			  • 25.00 - <30.00 (overweight/pre-obesity)
			  • ≥30.00 (obese)
			• Categories may be categorized as dichotomous variable (e.g., obese vs. not) based on data distribution

Family history of hemophilia at time of diagnosis (ever)	Yes	• Family has a history of hemophilia at the time of diagnosis	• Yes • No • Unknown
History of exposure to HCV infection (ever)	Yes	• Status HCV infection	• No infection (anti-HCV negative) • Active and/or cured infection
History of chronic liver disease (ever)	Yes	• Status chronic liver disease	• Not specified • Liver fibrosis • Liver cirrhosis child A • Liver cirrhosis child B • Liver cirrhosis child C • Categories will be finalized upon viewing the data distribution
Other comorbidities	Yes	• Other diseases	• Based on recording of “other diseases” field and free text specification of disease • Reporting of other comorbidities, categorization of diseases, and use of variable for analyses (e.g., inclusion in propensity score) will be based on actual data recorded; Due to the free text nature of the field and potential differential reporting between sites, data collected may not be analyzable
Target joints	Partially	• Localization • Location of target joint (anticipated added field to DHR)	• Yes/No • If localization = “target joint”, then target joints will = “yes” • Number of target joints, using location of target joint
AAV5 antibody status (ever)	Partially	• Has a test for vector antibodies been carried out • If yes: result	• AAV5 Tab- • AAV5 Tab+ • Note, the data captured in the DHR at the time of SAP drafting does not specify exact testing method utilized, nor AAV type. Therefore, spurious ‘positive’ findings may be recorded (e.g., AAV6 antibody

Variable	Currently captured in DHR	DHR data field name(s)	Operational definition/description
			presence, which is not relevant for eligibility for Roctavian)
Prophylaxis type (closest to index date)	Yes	• Preparation/ medicinal product	• FVIII only • Emicizumab • Any SoC prophylaxis • See Table 4 for drug classifications
Use of immuno-suppression (ever)	Yes	• Was immuno-suppression carried out due to the gene therapy	• For patients in Roctavian cohort, was immunosuppression used (yes/no)
FVIII infusion rate (before index date)	Yes (calculated)	• Preparation/ medicinal product • Frequency • Start of reporting period • End of reporting period	• Number of FVIII infusions during 12-month baseline period • If data allows, infusion rate will be derived based on the therapy usage and frequency of individual usage periods recorded in the DHR for any reason • Data is expected to be able to allow for summaries of AIR • To be calculated for FVIII separately (by class) from emicizumab
Prior FVIII utilization (before index date)	Yes (calculated)	• Occasion • Preparation/ medicinal product • Consumption/ delivered • Weight • Start of reporting period • End of reporting period	• Total IU during the baseline period and annual utilization of FVIII concentrates expressed as IU/kg/year • Total IUs received over the 12 months before index date divided by the weight (kg) closest to index date, stratified by occasion of use: bleed (suspected, spontaneous, or unknown hemorrhage), prophylaxis, short-term prophylaxis (intensified on-demand treatment), surgery, ITT, other/unknown • Calculate annualized metric of the FVIII usage multiplied by an individualized factor based on amount of prior history (e.g., if 26 weeks of history, multiply by 2), stratified by occasion of use: bleed (suspected, spontaneous, or unknown hemorrhage), prophylaxis, short-term prophylaxis (intensified on-demand treatment), surgery, ITT, other/unknown
Prior ABR (before index date)	Yes (calculated)	• Occasion • Therapy scheme • Severity • Localization • Start of reporting period • End of reporting period	• Using the most recent 12 months of pre-index data (when available), calculate ABR using number of prior bleeds within the reporting period start and stop dates ○ Note: a bleeding event is captured by occasion for therapy will be classified as any one of the following types of bleeds: ○ Suspected bleeding/hemorrhage ○ Spontaneous bleeding/hemorrhage ○ Bleeding/hemorrhage, cause unknown

Variable	Currently captured in DHR	DHR data field name(s)	Operational definition/description
			○ All three bleeding event categorizations will be included in the ABR calculation • Calculate annualized metric of the number of bleeding events multiplied by an individualized factor based on amount of prior history (e.g., if 26 weeks of history, multiply by 2) • ABR will be reported as total ABR, treated ABR (therapy scheme = “on-demand), major ABR (severity = “severe” or “life-threatening”), life-threatening ABR (severity = “life-threatening”), and joint ABR (localization = “joint”) • See further details in Table 5 for bleed definitions

Abbreviations: AAV: adeno-associated virus; ABR: annualized bleeding rate; AIR: annualized infusion/injection rate; BMI: body mass index; cm: centimeter; DHR: Deutsches Hämophilieregister; FVIII: coagulation factor VIII; HA: hemophilia A; HCV: hepatitis C virus; HTC: hemophilia treatment center; ITT: immune tolerant therapy; IU: international units; kg: kilogram; SoC: standard of care

Note: It is expected that variables that are not currently captured in the DHR or partially captured in the DHR will be fully captured at the time of the analysis.

7.4.2. Exposure Variables

Once inclusion and exclusion criteria are applied to the patient population, Table 5 will be used to identify index medications for the Roctavian and SoC cohorts. This table identifies all drug names as well as the frequency and dosage within each treatment group. Dosages are patient dependent, calculated based on the patient's weight. If weight is missing at the treatment date, methods described in Section 7.9.5.4 regarding missing weight will be used. Note, the index medication will be Roctavian administration for the Roctavian cohort and the prophylaxis administration closest to and before the study consent for the SoC cohort.

To account for any potential concerns regarding heterogeneity of SoC treatments, a sensitivity analysis is planned to analyze the SoC treatment types separately, as outlined in Section 7.9.5.3.

Treatment patterns, switching between SoC treatment classes (SHL, EHL, PD, and emicizumab), and switching between FVIII alone and FVIII and emicizumab during the study follow-up will be examined in the SoC cohort. If treatment switching between SoC classes is observed in >30% of the SoC cohort, patient characteristics and the primary outcome will be compared between patients who switched SoC treatment versus not to see if there are significant differences between these two SoC sub-cohorts (standardized mean difference (SMD) > 0.25 or clinically significant after reviewed by clinical experts). If significant differences of outcome between these two SoC sub-cohorts is detected, separate comparisons will be conducted between Roctavian cohort and two SoC sub-cohorts for all outcomes.

As noted in Section 7.3.3, patients in the SoC cohort who are administered Roctavian after study consent will be censored at the point in which they receive Roctavian.

Table 4: HA Treatments*

Treatment Type	Treatment Class	Treatment Name	Recommended Treatment Frequency and/or Dose
SoC	Emicizumab	Emicizumab (Hemlibra)	3 mg/kg once every week for the first 4 weeks; Then, 1.5 mg/kg once every week, 3 mg/kg every 2 weeks, or 6 mg/kg every 4 weeks
	SHL products	Kovaltry	20-40 IU/kg administered 2-3 times weekly
		Lonoctocog alfa (Afstyla)	20-50 IU/kg administered 2-3 times weekly
		Octocog alfa (Advate)	20-40 IU/kg every 2-3 days
		Moroctocog alfa (ReFacto)	20-40 IU/kg at intervals of 2-3 days
		Simoctocog alfa (Nuwiq)	20-40 IU/kg at intervals of 2-3 days
		Turoctocog alfa (NovoEight)	20-40 IU/kg administered every second day or 20-50 IU/kg administered 3 times weekly
	EHL products	Damoctocog alfa pegol (Jivi)	45-60 IU/kg every 5 days; Based on patient clinical characteristics, dose can also be 60 IU/kg every 7 days or 30-40 IU/kg 2 times per week; Maximum dose per injection for prophylaxis should not be higher than approximately 6000 IU
		Efmoroctocog alfa (Elocta)	50 IU/kg every 3-5 days; Dose may be adjusted to 25-65 IU/kg based on patient response

Treatment Type	Treatment Class	Treatment Name	Recommended Treatment Frequency and/or Dose
		Rurioctocog alfa pegol (Adynovi)	40-50 IU/kg twice weekly in 3–4-day intervals
		Turoctocog alfa pegol (Esperoct)	50 IU/kg every 4 days
	PD products	Voncento	20-40 IU/kg at intervals of 2-3 days
		Beriate	20-40 IU/kg at intervals of 2-3 days
		Octanate	20-40 IU/kg at intervals of 2-3 days
		Haemoctin	20-40 IU/kg at intervals of 2-3 days
		Faktor VIII SDH - Intersero	20-40 IU/kg at intervals of 2-3 days
Roctavian	N/A	Valoctocogene roxaparvovec (Roctavian)	6×10^{13} vg/kg body weight, administered as a single intravenous infusion

Abbreviations: EHL: extended half-life; IU: international units; kg: kilogram; mg: milligram; N/A: not applicable; PD: plasma-derived; SHL: standard half-life; SoC: standard of care; vg: vector genomes

*Note: During the analysis phase, the final list of SOC treatments are expected to be confirmed based on the patients enrolled in the study and their observed data; the final list will be updated for the final study report as necessary.

7.4.3. Outcome Variables

Primary and secondary outcomes specific to each objective are outlined in Table 5 below.

Table 5: Outcome Variables

Variable	Currently captured in DHR	DHR data field name(s)	Operational definition and calculation of outcome measures	Timepoints for data collection
Bleeding Events				

Treated ABR	Yes (calculated)	• Therapy scheme
		• Occasion
		• Date of bleed
		• Therapy start
		• End of therapy
			• Number of treated bleeding events per year
			• Calculate ABR using number of treated bleed events within the relevant time period (≥1 year of follow-up, ≥2 years of follow-up, ≥3 years of follow-up, all available follow-up)
			  • A bleeding event is captured by occasion for therapy and will be classified as any one of the following types of bleeds:
			  ○ Suspected bleeding/hemorrhage
			  ○ Spontaneous bleeding/hemorrhage
			  ○ Bleeding/hemorrhage, cause unknown
			  ○ All three bleeding event categorizations will be included in the ABR calculation
			• Bleeds will be identified as treated bleeds if they meet one of the following criteria:
			  ○ If bleed date is within 3 calendar days of treatment date where occasion for treatment is one of the hemorrhage values OR therapy scheme is “on demand”
			  ○ If multiple bleeds with different localization occur on the same calendar day of the last bleed before treatment for bleed, the subsequent treatment within 3 calendar days is considered to pair with each of these bleeds; Each of these bleeds that is within 3 calendar days of the subsequent treatment is therefore considered to be a treated bleed
			  ○ Two bleeds of the same localization are considered to be one bleed if the second occurs within 3 calendar days from the date of the last treatment for the first bleed; The last treatment is defined
				• ≥1 year
				• ≥2 years
				• ≥3 years
				• All available follow-up

Variable	Currently captured in DHR	DHR data field name(s)	Operational definition and calculation of outcome measures	Timepoints for data collection
			as the last treatment before a new bleed occurs, either in the same or in a different location regardless of whether the second bleed is followed by a treatment • Calculate annualized metric of the number of bleeding events by dividing the number of bleeds by the number of days in the relevant time period, multiplied by 365.25	
Major ABR	Yes (calculated)	• Occasion • Severity • Date of bleed	• Number of major bleeding events per year • Calculate ABR using number of bleed events within the relevant time period (≥1 year of follow-up, ≥2 years of follow-up, ≥3 years of follow-up, all available follow-up) • Major bleeds are defined based on “severe” or “life-threatening” (irrespective of location) reported in bleed severity ○ Note: a bleeding event is captured by occasion for therapy will be classified as any one of the following types of bleeds: ○ Suspected bleeding/hemorrhage ○ Spontaneous bleeding/hemorrhage ○ Bleeding/hemorrhage, cause unknown ○ All three bleeding event categorizations will be included in the ABR calculation • Calculate annualized metric of the number of bleeding events by dividing the number of bleeds by the number of days in the relevant time period, multiplied by 365.25	• ≥1 year • ≥2 years • ≥3 years • All available follow-up
Life-threatening ABR	Yes (calculated)	• Occasion • Severity • Date of bleed	• Number of life-threatening bleeding events per year • Calculate ABR using number of bleed events within the relevant time period (≥1 year of follow-up, ≥2 years of follow-up, ≥3 years of follow-up, all available follow-up) • Life-threatening bleeds are defined based on “life-threatening” (irrespective of location) reported in bleed severity ○ Note: a bleeding event is captured by occasion for therapy will be classified as any one of the following types of bleeds: ○ Suspected bleeding/hemorrhage ○ Spontaneous bleeding/hemorrhage	• ≥1 year • ≥2 years • ≥3 years • All available follow-up

Variable	Currently captured in DHR	DHR data field name(s)	Operational definition and calculation of outcome measures	Timepoints for data collection
			○ Bleeding/hemorrhage, cause unknown ○ All three bleeding event categorizations will be included in the ABR calculation • Calculate annualized metric of the number of bleeding events by dividing the number of bleeds by the number of days in the relevant time period, multiplied by 365.25	
Joint ABR	Yes (calculated)	• Occasion • Localization • Date of bleed	• Number of joint bleeding events per year • Calculate ABR using number of bleed events within the relevant time period (≥1 year of follow-up, ≥2 years of follow-up, ≥3 years of follow-up, all available follow-up) • Joint bleeds are defined based on localization of bleed ○ Note: a bleeding event is captured by occasion for therapy will be classified as any one of the following types of bleeds: ○ Suspected bleeding/hemorrhage ○ Spontaneous bleeding/hemorrhage ○ Bleeding/hemorrhage, cause unknown ○ All three bleeding event categorizations will be included in the ABR calculation • Calculate annualized metric of the number of bleeding events by dividing the number of bleeds by the number of days in the relevant time period, multiplied by 365.25	• ≥1 year • ≥2 years • ≥3 years • All available follow-up
% Zero treated bleeds	Yes (calculated)	• Therapy scheme • Occasion • Start of reporting period • End of reporting period	• % Of patients with zero treated bleeds calculated based on treated bleeding • No bleeding events captured within the reporting period start and stop dates • The number of patients in the Roctavian cohort with zero treated bleeds is divided by the total number of patients in the Roctavian cohort • The same calculation will be used for the SoC cohort • See definition for treated bleed above to be used to derive this variable	• ≥1 year • ≥2 years • ≥3 years • All available follow-up
% Zero major bleeds	Yes (calculated)	• Occasion • Severity	• % Of patients with zero major bleeds calculated based on major bleeding • No bleeding events captured within the reporting period start and stop dates	• ≥1 year • ≥2 years • ≥3 years

Variable	Currently captured in DHR	DHR data field name(s)	Operational definition and calculation of outcome measures	Timepoints for data collection
		• Start of reporting period • End of reporting period	• The number of patients in the Roctavian cohort with zero major bleeds is divided by the total number of patients in the Roctavian cohort • The same calculation will be used for the SoC cohort • See definition for major bleed above to be used to derive this variable	• All available follow-up
% Zero life-threatening bleeds	Yes (calculated)	• Occasion • Severity • Start of reporting period • End of reporting period	• % Of patients with zero life-threatening bleeds calculated based on life-threatening bleeding • No bleeding events captured within the reporting period start and stop dates • The number of patients in the Roctavian cohort with zero life-threatening bleeds is divided by the total number of patients in the Roctavian cohort • The same calculation will be used for the SoC cohort • See definition for life-threatening bleed above to be used to derive this variable	• ≥1 year • ≥2 years • ≥3 years • All available follow-up
% Zero joint bleeds	Yes (calculated)	• Occasion • Localization • Start of reporting period • End of reporting period	• % Of patients with zero joint bleeds calculated based on joint bleeding • No bleeding events captured within the reporting period start and stop dates • The number of patients in the Roctavian cohort with zero joint bleeds is divided by the total number of patients in the Roctavian cohort • The same calculation will be used for the SoC cohort • See definition for joint bleed above to be used to derive this variable	• ≥1 year • ≥2 years • ≥3 years • All available follow-up
Treatment Outcomes				
Use of any hemostatic treatments	Yes	• Preparation/medicinal product • Start of reporting period • End of reporting period	• Patients with any hemostatic medication use during the follow-up period	• ≥1 year • ≥2 years • ≥3 years • All available follow-up
Prophylactic hemostatic treatments	Yes (calculated)	• Occasion • Preparation/medicinal product • Weight	• Amount of prophylactic hemostatic treatments utilized per patient over time (IU or mg), as well as per patient per kg over time (IU/kg) for FVIII products and mg/kg for emicizumab	• ≥1 year • ≥2 years • ≥3 years

Variable	Currently captured in DHR	DHR data field name(s)	Operational definition and calculation of outcome measures	Timepoints for data collection
		• Consumption/delivery • Treatment date • Start of reporting period • End of reporting period		• All available follow-up
On-demand hemostatic treatments	Yes (calculated)	• Occasion • Preparation/medicinal product • Weight • Consumption/delivery • Treatment date • Start of reporting period • End of reporting period	• Amount of on-demand FVIII utilized per patient over time (IU or mg), as well as per patient per kg over time (IU/kg) for FVIII products and mg/kg for emicizumab for a bleeding event (occasion = “suspected hemorrhage”, “spontaneous hemorrhage”, or “hemorrhage, cause unknown”) • Amount of on-demand FVIII utilized per patient over time (IU or mg), as well as per patient per kg over time (IU/kg) for FVIII products and mg/kg for emicizumab for short-term prophylaxis (occasion = “intensified on-demand treatment (=short-term prophylaxis)”)	• ≥1 year • ≥2 years • ≥3 years • All available follow-up
FVIII Infusion/ injection rate	Yes (calculated)	• Preparation/ medicinal product • Frequency • Start of reporting period • End of reporting period	• Number of infusions/injections during the follow-up period • If data allows, infusion/injection rate will be derived based on the therapy usage and frequency of use during individual usage periods recorded in the DHR for any reason • Data is expected to be able to allow for summaries of AIR	• ≥1 year • ≥2 years • ≥3 years All available follow-up

Time to resumption of prophylactic treatment	Yes (calculated)	• Date of gene therapy
		• Occasion
		• Preparation/medicinal product
		• Treatment date
			• Roctavian cohort only
			• Treatment date of resumption of prophylaxis defined as at least three consecutive months of prophylaxis and at least one of the following:
			  • 4 doses of emicizumab
			  • 18 doses of EHL
			  • 24 doses of SHL and/or PD
			• Note, further refinement of this variable will be explored at the analysis phase based on observed data to account for the products being used by
				All available follow-up

Variable	Currently captured in DHR	DHR data field name(s)	Operational definition and calculation of outcome measures	Timepoints for data collection
			the patients (accounting for any new products on the market); Alternative definitions, such as, at least 2 times per week of SHL and 1 time per week for EHL during the 3-month period may be explored as necessary • Definition utilized in this study is relevant to the fields that the DHR collects and will be aligned as best as possible to other definitions utilized external to this study	
Clinical Outcome Assessments				
HJHS	Yes (calculated)	• Date of the joint score • Score used • Joint score	• For each patient, the HJHS domains are expected to be collected at baseline (index date) and every 6 months during the follow-up period • The change from baseline will be calculated and a repeated measures model will be used to account for the scores at different time points • HJHS are calculated for the left and right elbow, left and right knee, and left and right ankle, as well as a global gait score; Scores will be calculated for each joint and for the global gait score	All available follow-up
Haemo-QoL-A	No		• For each patient, the Haemo-QoL-A domains are expected to be collected at the baseline and every 6 months during the follow-up period • The change from baseline will be calculated and a repeated measures model will be used to account for the scores at different time points • Haemo-QoL-A scores are calculated for six different domains (physical functioning, role functioning, worry, consequences of bleeding, emotional impact and treatment concerns); Scores will be calculated for each of these six domains • A total Haemo-QoL-A score including all six domains will also be calculated.	All available follow-up
BPI-sf	No		• For each patient, the BPI-sf score is expected to be collected at the baseline and every 6 months during the follow-up period • The change from baseline will be calculated and a repeated measures model will be used to account for the scores at different time points • BPI-sf measures will be reported for pain intensity (Question 5 of BPI-sf that describes patients' pain on average) and pain interference (average of the seven subitems of Question 9 of BPI-sf)	All available follow-up
Safety Outcomes				

Variable	Currently captured in DHR	DHR data field name(s)	Operational definition and calculation of outcome measures	Timepoints for data collection
All cause death	Yes	• Reason for resignation • Date of retirement	• Any patients with reason for resignation from DHR as “deceased”	All available follow-up
Hemophilia-related death	Yes	• Reason for resignation • Cause of death • Date of retirement	• If reason for resignation from DHR is “deceased” and cause of death is captured as “hemophilia-related”	All available follow-up
AEs leading to hospitalization and death	Partially	• Medically relevant events in this reporting period • Connection with hemophilia treatment • Adverse events leading to hospitalization or death	• To define AEs, any medically relevant event, if connection with hemophilia treatment = yes • To define AEs leading to hospitalization and death, proposed additional field of “adverse events leading to hospitalization or death” will be used	All available follow-up
Development of FVIII inhibitors	Yes (calculated)	• Inhibitor tests against FVIII/FIX positive in this reporting period • Date of the inhibitor test • Titer • Test assay used	• If inhibitor tests against FVIII/FIX were performed during the reporting period, patients with a positive test will be identified • Based on any recording of the DHR variables for inhibitors developed during the reporting period, positive inhibitor tests during the reporting period, or use of ITT • Exclusion will be based upon either 2 positive inhibitor tests during the reporting period or 1 positive inhibitor test and use of ITT during the reporting period • Titer values (BU/ml) based on the test assay used will be assessed to validate the positive test; A value <0.5 BU/ml will be used to identify presence of inhibitors	All available follow-up
Thrombo-embolic events	Yes	• Other relevant event	• Other relevant event = thromboembolic event	All available follow-up

Variable	Currently captured in DHR	DHR data field name(s)	Operational definition and calculation of outcome measures	Timepoints for data collection
New malignant neoplasms	Yes	• Other relevant event	• Other relevant event = other; Free text field indicates new malignant neoplasm	All available follow-up

Severe liver disease	Yes	• Other relevant event
		• Status chronic liver disease
			• Other relevant event = other; Free text field indicates liver disease
			• Liver failure or cirrhosis, as defined by one of the chronic liver disease values:
			  ○ Liver fibrosis
			  ○ Liver cirrhosis child A
			  ○ Liver cirrhosis child B
			  ○ Liver cirrhosis child C
			• Definition may be refined upon viewing the data distribution
				All available follow-up

Abbreviations: AbD: Anwendungsbegleitende Datenerhebung; ABR: annualized bleeding rate; AE: adverse event; AIR: annualized infusion/injection rate; BPI-sf: Brief Pain Inventory-short form; BU/ml: Bethesda unit/milliliter; DHR: Deutsches Hämophilieregister; ED: exposure days; FVIII: coagulation factor VIII; FIX: coagulation factor IX; HJHS: Hemophilia Joint Health Score; IU: international unit; ITT: immune tolerant therapy; kg: kilogram; MCID: minimal clinical important difference; mg: milligram; PRO: patient reported outcome; QoL: quality of life; SoC: standard of care.

Note: It is expected that variables that are not currently captured in the DHR or partially captured in the DHR will be fully captured at the time of the analysis.

7.5. Data Sources

7.5.1. Deutsches Hämophilieregister

This study will leverage data from the DHR, a clinical German registry maintained by the Paul-Ehrlich-Institute in cooperation with the Gesellschaft für Thrombose- und Hämostaseforschung e. V. (GTH), the Deutsche Hämophiliegesellschaft zur Bekämpfung von Blutungskrankheiten e. V. (DHG) and the Interessengemeinschaft Hämophiler e. V. (IGH).[11] It is a registry for medical research and quality assurance in the care of persons with hemophilia A, hemophilia B, von Willebrand syndrome or other coagulation factor deficiencies. Medical data of patients with hemostasis disorders are compiled in the DHR. It has been in operation since December 2008. About 130 institutions report data from a total of almost 8,500 affected persons every year.[12]

As a clinical patient registry, the DHR represents a systematic collection of data, i.e., standardized medical documentation, which makes data more comparable and thus evaluable in order to answer questions relevant to practice. As hemophilia is a rare disease, a registry is of particular importance: large-scale studies are often difficult to conduct in this field, as there are simply not enough patients to make reliable statements. Therefore, the strength of a registry lies in the possibility of long-term observation of the disease and its treatment in order to be able to draw meaningful conclusions.

The legislator has recognized this and, with an extension of the Transfusion Act (Transfusionsgesetz, TFG), has given the DHR a special status with a legal basis. Data collection in the DHR is now mandatory and all treating physicians are obliged to inform their patients about participation in the DHR.

Patients consent to their data being included in the DHR. Baseline information is collected including demographic characteristics and baseline history. Other information including treatments, clinical outcome assessments (COAs), and bleeding events are expected to be recorded at least two times per year. For patients who do not consent, minimal anonymous data is collected. As of 2018, there were 4,240 patients with HA included in the DHR, 2,583 of whom had severe HA. This represents 104% of expected cases of severe HA in Germany, using an average prevalence of 6.0 cases of severe HA per 100,000 males and a German population of 83 million.[1, 13]

7.6. Study Sample Size

The primary goal of HA treatment is to reduce the bleeding rate or to achieve freedom from bleeding. As an approximation of the appropriate number of cases for the data collection accompanying the application, the Institute for Quality and Efficiency in Health Care (IQWiG) conducted the sample size calculation based on ABR for treated bleeds. Evaluation of the ABR is performed using a negative binomial model. The relative effect measure is the incidence rate ratio of Roctavian over SoC, which can be tested against the shifted null hypothesis of 0.5, assuming a significance level alpha =2.5% with a one-sided test, and power of at least 80%. Higher values for the ABR (parameter λ) stand for a worse outcome. Furthermore, a distribution of the Sample Roctavian vs. SoC of 1:5 is assumed (sample size ratio θ = 0.2). Other required parameters are the Average Exposure Time (u_t= 1 year), the ABR for the SoC and Roctavian groups (λ_{SoC}= 3, $\lambda_{\text{Roctavian}}$= 0.85) and a value for the overdispersion (ϕ = 1.5). This results in a total sample size of at least 397 patients (Roctavian cohort n = 67, control cohort n = 330).

Based on current estimates of patient enrolment, the study will be powered based on the ABR approach. Therefore, we support and accept G-BA's ABR based approach for sample size justification, where the target sample size will be at least 397 patients in total with 1 and up to 5

Roctavian and comparison cohort patients (Roctavian cohort n =67, comparison cohort n=330). The sample size calculation is based on a shifted null hypothesis to add robustness to the generated evidence. However, the actual null hypotheses for testing all primary and secondary endpoints are not shifted.

7.7. Data Management

All data for this study will be collected and stored in the DHR. Study site personnel is responsible for patient data collection and data entry into the DHR. Validation of patient data in the clinical database will be carried out via automated edit checks as well as manual checks raised by clinical research associates during on-site routine monitoring visits. BioMarin will request data cuts from the DHR at specified intervals to assess data six months after the study start date, 18 months after the study start date, and subsequent 18-month intervals for the duration of the study period. Note that the actual data cuts will be requested earlier so that interim reports can be completed as scheduled. These data cuts will be sent directly to [redacted] for analysis. All data are stored on secure servers and are auto-archived and password-protected for any future access requirements. Study documents are retained in a minimum of two secure locations and are only removed or deleted upon sponsor-written request.

7.7.1. Statistical Software

SAS® software (SAS Institute Inc., Cary, North Carolina, United States [US]) version 9.4 or higher will be used to manage the analytic datasets and conduct data analyses. The R survival package (version 3.2-13 or higher; R version 3.5.2) may be used to conduct weighted survival analysis and additional analyses.

7.7.2. Data Protection

Measures will be taken to ensure the privacy of subject data, including the use of subject numbers in the DHR. A list linking subject identification numbers with subject names and other personal information will be kept in a secure place, separate from the subjects' medical records. BioMarin will follow all applicable regulations and guidelines in the relevant locality, country, and/or region to protect the privacy of subject data.

Subjects are expected to have a unique identifier based on a de-identified study center code and unique patient code (e.g., patient at study center A may be identified as A-101). Any subject records or datasets that are transferred to the sponsor will contain the identifier only; subject names or any information which would make the subject identifiable will not be transferred. Study centers that patients are seen at will not be identifiable.

The subject must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the subject, who will be required to give consent for their data to be used as described in the informed consent.

The subject must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate Institutional Review Board (IRB)/independent ethics committee (IEC) members, and by inspectors from regulatory authorities.

In the event of a data security breach, participating institutions, study vendors, and/or BioMarin will take appropriate action according to their local processes and report to appropriate regulatory agency(ies) according to applicable laws and regulations.

7.8. Propensity Score Methodology

Based on the prospective cohort study design, heterogeneity of covariates among the Roctavian and SoC cohorts will be accounted for by propensity score methods. The primary analysis will be centered around standardized mortality ratio weighting (SMRW) and a sensitivity analysis using the propensity score matching (PSM) method will only be conducted to explore the robustness of the primary analysis results using SMRW. After generating rebalanced cohorts using the SMRW method, descriptive analyses will assess the balance of covariates between the two cohorts. If cohorts are still imbalanced after both approaches, additional covariates and/or interaction terms between the covariates will be explored and included in the propensity score model and/or adjusted for in the main analyses.

7.8.1. Estimation of the Propensity Score

In the absence of randomized controlled trial data, propensity score methods are commonly used to account for heterogeneities in baseline covariates that may exist among multiple patient cohorts. In this section, the methodology of propensity score estimation is described.

Propensity scores will be calculated for patients in the Roctavian and the SoC cohorts to balance covariates and obtain an unbiased estimate of the treatment effect. Propensity score is the probability of each subject being assigned to Roctavian, conditional on the key prognostic factors included in the model. Propensity scores will be estimated by fitting a multivariable logistic regression model that includes the key prognostic factors (described in Section 7.8.2) as covariates. The cohort indicator (Roctavian cohort (Y=1) or SoC cohort(Y=0)) will be used as the dependent variables. The logistic regression model is mathematically expressed as

$$\log it\,(\Pr(Y = 1)) = X'\beta,$$

where logit(·) represents the logit function and X represents the vector of prognostic factors. After the model fit, propensity scores will be generated for all patients without missing values in any prognostic factors included in the model for subsequent analyses. The logit transformed propensity score (LTPS) is considered associated with preferred statistical properties (e.g., approximately normally distributed) over the raw propensity score and is therefore often used in applications of PSM methods.

All variables listed in Table 3 will be assessed as prespecified candidate covariates for inclusion in the propensity score models. Therefore, assuming the target enrolment of n=67 Roctavian participants, a maximum of 6 parameters will be included in the model. If fewer than 67 Roctavian participants are enrolled, the same approach will be applied to determine the number of parameters that can be included in the model.

Note the list of prespecified candidate covariates included in the propensity score models will be finalized during the interim report(s) and will be confirmed based on a literature review of factors associated with bleeding (specifically focused on literature from Germany), previous propensity score development for a comparison of Roctavian to FVIII prophylaxis based on studies that were part of the Roctavian clinical development, expert opinion from health care practitioners in Germany managing PwSHA, data availability, model assessment, and sample size, which are described in Section 7.8.2. In addition, covariate selection will be explored as a sensitivity analysis (Section 7.9.5.2).

For each logistic regression model, parameter estimates of the covariates and their standard errors, odds ratio (OR) and their two-sided Wald 95% confidence interval (CI) will be presented for continuous variables and the non-reference levels of categorical variables. P-values for each corresponding OR and for each parameter will be presented. The number of patients in each category level will be presented, as well as the total number of patients with non-missing data for each continuous variable (which by construction will equal the number of patients in the model).

Propensity scores will be generated once for the primary outcome, rather than several iterations for each outcome. If imbalance remains in covariates for specific outcome analyses, further adjustment will be applied in the corresponding regression models.

7.8.2. Variable Identification for Propensity Score Model

7.8.2.1. Variable Identification Based on Previous Work

Prior to the initial data cut for the interim analysis at 18 months after study initiation, a literature review will be conducted to identify potential variables for inclusion in the propensity score. The literature review will focus on data published from Germany describing the bleeding events among people with HA and PwSHA. Additionally, previous work to develop propensity scores for a comparison of Roctavian to FVIII prophylaxis based on studies that were part of the Roctavian clinical development will inform potential variables.[14]

7.8.2.2. Variables Collected in the DHR

Variables identified in the literature, as well as based on clinical input, will be compared to the variables currently collected in the DHR for consideration in the PS. Based on previous propensity score development work, it is expected the DHR currently collects the key variables that would be included in a propensity score.[14] These variables include: age, BMI, HTC/site, target joints, baseline ABR, baseline FVIII utilization and baseline prophylaxis class (SHL, EHL, PD, emicizumab).

7.8.2.3. Clinical Input into Propensity Score

Healthcare practitioners in Germany managing PwSHA and treating PwSHA with either Roctavian or SoC products will advise the study team regarding overall study conduct and interpretation, as well as input regarding variables identified for propensity score inclusion. Healthcare practitioners are expected to provide input into variables both associated with the endpoint of bleeding events as well as factors associated with choosing Roctavian treatment.

7.8.2.4. Baseline Comparison of Groups for Propensity Score Development

Patient characteristics will be presented for all baseline variables described in Table 3 and Table 4, along with tests for difference using appropriate statistical testing; Welch's t-test for continuous variables, and the Chi-square test for categorical variables.

SMD will be calculated for continuous and categorical variables. SMD represents the most commonly used statistic to examine the balance of covariate distribution between groups, with a value greater than 0.1 indicating some imbalance between groups and > 0.25 indicating poor imbalance, where the model should either be improved or rejected in favor of an alternative model.[15] If imbalance of > 0.25 remains, the propensity score model will be refined by adding additional covariates, adding interaction terms and/or conducting appropriate transformation of the covariates (squared, log, etc.). Any covariates that remain imbalanced after further refinement of the propensity score model will be included in the regression model (for model-based analyses – i.e., bleeding events) to estimate the average treatment effect on the outcome.

After propensity score methods have been applied, tabulations will be repeated with p-values and SMDs re-calculated to investigate any meaningful differences remaining after propensity score-adjustment, both in the characteristics included in the propensity scoring, and also those not included. Although all baseline characteristics will be presented for completeness, the balance of the variables

included within the propensity score models will be the focus due to the importance assigned to these characteristics.

In accordance with guidance that model-evaluation tools of the logistic regression are secondary to the balancing of participant characteristics,[16, 17] sensitivity analyses will also be performed with the omission of highly correlated variables. Collinearity among covariates that are used to generate weighting from the SMRW method will be assessed by the variance inflation factor (VIF) and conditional index. A conditional index > 10 indicates that high collinearity exists among some of the covariates. VIF will also be checked to confirm collinearity, with VIF > 5 as moderate and VIF > 10 as high collinearity. If high collinearity is detected, a sensitivity analysis will be conducted by dropping the covariate(s) that are responsible for the high collinearity until the conditional index for all covariates drops to 10 or below, and then recreate the weights and refit the SMRW model for the primary outcome. Results will be compared with those from models using weights generated from the full set of covariates to assess the robustness of the primary results.

7.8.3. Application of the Propensity Score

In the Sections below, SMRW and PSM methods are described, and considerations for choosing the SMRW as the primary analytical method, with PSM as an *a priori* sensitivity analysis are outlined.

7.8.3.1. Standardized Mortality Ratio Weighting

The SMRW approach is to reweight the SoC cohort to match the characteristics of the treated (e.g., Roctavian) cohort,[18] which provides an estimate of the average treatment effect in the Roctavian cohort instead of in the overall treated and control cohorts combined. This method allows for the preservation of results for the Roctavian cohort. SMRW is particularly useful when the Roctavian cohort will be compared with multiple sub-cohorts of patients who receive SoC, without reweighting the Roctavian cohort for each subgroup analysis. In addition, this method is advantageous when the sample size of the treatment cohort (Roctavian cohort) is small. For the Roctavian cohort, the weight, W, assigned in the SMRW method for each individual *i*, based on propensity score, P_i, is:

$$W_i = 1$$

For the SoC cohort, patients receive weights of:

$$W_i = P_i / (1-P_i)$$

The resulting analysis will have the control cohort reweighted to match the treated cohort. A weakness of SMRW method is it is subject to extreme weights. Use of a robust variance estimator is strongly recommended. Weight trimming might be needed to address extreme weights and prevent variance inflation.[19, 20]

7.8.3.2. Propensity Score Matching

The PSM method matches each subject in the treated cohort with a subject in the SoC cohort exhibiting the nearest propensity score (this is also known colloquially as ‘greedy’ matching) without replacement. Consequently, if all patients from the smallest group (i.e., Roctavian or SoC) are matched, then the sample size for the patients included in subsequent analysis becomes double the sample size of the smallest group of unpaired patients. If an appropriate match is not available, for example due to a lack of overlap in propensity score values between groups, then cases are discarded and the matched sample size for analysis is reduced accordingly. Where possible, analyses will be repeated with replacement to enable matching of all patients, without reductions in the overall sample size due to discrepancies between patient numbers in each group. Any analyses involving

replacement will report the number of repeated histories as an additional outcome measure. Should the number of 'repeated' matches exceed 20% of the total, the analysis will be run without replacement to avoid reliance on a small number of patients. For the PSM, a caliper width of 0.2 times the SD of the propensity score will be used and 'random' order.[21] To give confidence in the robustness of the results, a second analysis will be performed using a 'tight' caliper, of 0.01. The covariate distributions between the Roctavian and the SoC cohorts will be reassessed based on each method used for matching.[20]

7.8.4. Comparison of Propensity Score Methods

Presented below is a summary of considerations for the use of SMRW and PSM methods, described above.

Table 6: Considerations for SMRW versus PSM Methods

Propensity Score Method	Considerations
SMRW	• Include all participants • The target population is the treated population • Allows preservation of the results in the treatment cohort (e.g., Roctavian cohort) and weighing of the comparator cohort to the observed real-world characteristics of the treatment cohort • Subject to extreme weighting.
PSM	• Only include participants who are successfully matched. • Successful matching can be challenging if the study cohort sample sizes are small. • Analysis can be more interpretable to the scientific community as the inclusion of only matched participants mirrors randomized clinical trial designs.

Abbreviations: PSM: propensity score model; SMRW: standardized mortality ratio weighting.

Besides SMRW and PSM, inverse probability of treatment weighting (IPTW) with average treatment effect (ATE) was also considered as a propensity score weighting methodology. In contrast to the SMRW approach, which apply weights to the control cohort, IPTW apply weights to both the treated and the control cohort, thus the treated cohort is not preserved, and reweighting is required when comparing the treated cohort to different subgroup of the controls (thus complicating the interpretation of results). Given the patients in the SoC cohort receive different classes of SoC treatment and the sensitivity analysis planned to compare the outcomes between the Roctavian cohort and the SoC sub-cohorts, SMRW was chosen as the primary propensity score weighting methodology over IPTW. In addition, IPTW estimates the average treatment effect in the total cohort while SMRW estimates the average treatment effect in the treated cohort. The results are expected to be different among the Roctavian and SoC cohorts, therefore, IPTW was not considered further for this study.

SMRW is proposed as the primary analysis to re-weight the baseline characteristics of the SoC cohort to reflect the Roctavian cohort more accurately.[19, 20] SMRW is preferred to PSM as it creates more balanced Roctavian and control sub-cohorts without re-weighting the Roctavian cohort, which increases interpretability of the analysis by ensuring consistency in reporting of sample size, baseline characteristics, and outcomes. Furthermore, the use of weighting (rather than matching) ensures that the entire sample for the Roctavian cohort is used to inform the comparative effectiveness, which increases statistical power.

A weakness of SMRW is the assignment of extreme weights for patients who have uncommon characteristics, which may bias the estimator and induce excessive variance. The distribution of weights will be plotted to visually check any noticeable outliers or extreme values. Outliers of the weights will also be assessed using methods described in Section 7.9.7. If extreme weights are detected, characteristics of the patients will be checked to make sure implausible values of the

covariates are not used in propensity score estimation. Given limited sample sizes, weight winsorization will be implemented by replacing the propensity score weight to the value at the 95th percentile for patients who had a propensity score weight greater than the 95th percentile in the control cohort.[22, 23] Sensitivity analyses will be conducted using PSM (see Section 7.9.5.2) to compare with results from the SMRW approach.

If the SMRW requires weight winsorization due to extreme weighting to balance the propensity score distributions between the Roctavian and SoC cohorts, and if the PSM sensitivity analysis is able to match 95% of the Roctavian population to at least three SoC controls, the PSM approach will be reported as the primary analytical method for all analyses.

7.8.4.1. Graphical Presentation of Propensity Score Diagnostics

The distribution of the propensity scores will be presented before and after weighting using histograms and density plots, and the c-statistic will be reported. Balance plots for the patient covariates included in the model will present the standardized differences before and after weighting and/or matching.

7.9. Statistical Analysis Approaches

Descriptive statistics will be generated for all study measures. Descriptive statistics will include means, 95% CIs, SDs, medians, interquartile range (IQR), and minimum and maximum values for continuous variables and frequencies and percentages for the categorical variables. Univariate statistics will be calculated for each measure of interest. Baseline and outcome variables will be compared between the Roctavian and SoC cohorts using chi-square tests for categorical variables, two-sided t-tests for continuous variables, and Wilcoxon rank-sum tests for medians of continuous variables if the continuous variables are not normally distributed.

For event-based outcomes including the bleeding outcomes, negative binomial models will be fit. Zero-inflated negative binomial models will also be considered if the outcomes show excess zeros. For binary outcomes, logistic regressions will be fit. For continuous outcomes, general linear regression will be used, with appropriate transformation if needed to ensure model assumptions are me. For COAs, general linear mixed models to account for repeated measures are planned. All the models will be adjusted with propensity score weights and results will be reported based on observed values (before SMRW is applied) and the weighted values (after SMRW is applied).

To adjust for confounding, propensity scores will be calculated and applied using appropriate propensity score SMRW to ensure balance of covariates between the Roctavian and SoC cohorts. Both unadjusted and propensity score adjusted results will be reported. SMRW is the primary propensity score method for adjustment of confounding. PSM will be performed as a sensitivity analysis to assess the robustness of the results from the primary SMRW analysis (see Section 7.9.5.2 for details). Additional details on propensity score methodology is presented in Section 7.7. If additional covariate adjustment is required to balance the cohorts, multivariable models will be reported.

P-values and SMDs will be reported for comparisons between Roctavian and SoC cohorts. A p-value <0.05 will be considered statistically significant. All analyses will be based on observed, not projected, data.

7.9.1. Patient Attrition

Patients meeting the inclusion criteria and not meeting the exclusion criteria will be summarized using frequency and percentage for the cohort selected. A STROBE flow diagram[24] will be used to visualize

sample size retainment at each step of the inclusion and exclusion criteria for the study population and cohort assignment.

Patient attrition will also be described for specific outcomes that are not assessed on the full patient population (e.g., attrition of patients who are not included in COA analyses due to missing data).

7.9.2. Analysis of Baseline Characteristics

Descriptive analysis will be conducted to describe baseline demographic and clinical characteristics of the Roctavian and SoC cohorts. See Table 3 for a list of all variables that will be described for the two cohorts. The baseline characteristics will capture data up but before the index date.

Measures of central tendency and dispersion (mean, SD, median) will be calculated and reported for continuous variables for each cohort. Continuous variables may be categorized into intervals, with the distribution of patients (n, %) provided. Independent sample t-tests for mean values and Wilcoxon rank-sum tests for median values will be performed as a comparison between the Roctavian and SoC cohorts.

For categorical variables, distributions and frequencies will be compiled and reported. Data will include the frequency (n, %) of total patients observed in each category. Chi-square tests will be performed as a comparison between the Roctavian and SoC cohorts.

SMD will be calculated for both continuous and categorical variables. SMD represents a commonly used statistic to examine the balance of covariate distribution between groups, with a value greater than 0.1 indicating some imbalance between groups, and SMDs >0.25 indicating poor balance.[25]

Patient characteristics will be presented for all patients prior to weighting (for Roctavian and SoC cohorts separately), overall, and for subgroups and sensitivity analyses where appropriate.

7.9.3. Analysis of Primary Outcome

Population	Measurement Period	Analysis Notes
All patients For interim and analyses at fixed timepoints, only those with specified amounts of follow-up will be included	≥1 year of follow-up, ≥2 years of follow-up, ≥3 years of follow-up, all available follow-up	Patients with no bleeds will be included as having an ABR of 0

The primary objective to compare the ABR for treated bleeds between the Roctavian and SoC cohorts will be measured by annualizing the number of bleeds reported in the DHR. Follow-up for ABR will begin as of the index date for the SoC cohort. For the Roctavian cohort, follow-up will begin based on whichever occurs latest: five weeks post-Roctavian infusion, three days after the last routine FVIII prophylaxis, or the beginning of 27 weeks after the last emicizumab injection. Bleeds will be identified if patients have an “occasion” of suspected bleeding, spontaneous bleeding, or bleeding, cause unknown. Patients may have multiple bleeds during the reporting period. To calculate ABR, a count of the number of bleeds for each patient will be divided by the number of days in the relevant time period for each patient, multiplied by 365.25. The mean of the individual ABRs for each cohort will be calculated and then compared between cohorts over the full follow-up time, as well as during annual increments during the follow-up. For analyses of annual increments, only those patients with full follow-up for that timepoint will be included. For example, analyses comparing ABRs during the first year will only include participants with ≥1 year of follow-up after the index date or analyses comparing ABRs through two years of follow-up will only include participants with ≥2 year of follow-up after the index date. Sample sizes are expected to be reduced in analyses of annual increments for interim analyses as data collection will be ongoing, and potentially reduce for final analyses due to censoring.

Follow-up for ABRs will be censored for the analysis based the earliest date after index of withdrawal, loss to follow-up, enrollment of an interventional hemophilia clinical trial, death, end of reporting/follow-up period in the DHR, or end of study follow-up, defined as the index date plus 1,095 days).

- For the Roctavian cohort**:** Participant returns to hemostatic prophylaxis (defined as at least three consecutive months of prophylaxis and at least one of the following: 4 doses of emicizumab, 18 doses of EHL, or 24 doses of SHL and/or PD). After return to hemostatic prophylaxis is identified, the date of the first administration of prophylactic therapy in the consecutive 3-month period will be utilized as the censoring date.
- For the SoC cohort: Participants will additionally be censored if administered Roctavian or another HA gene therapy (if available commercially).

Mean, SD, median, IQR, minimum and maximum will be reported for the primary outcome by study group. Histograms will be plotted for the primary outcome by study group. SMD will be calculated to compare Roctavian and SoC cohort. The patient number in the SoC group will be weighted using SWRW generated from the propensity score model. Both unadjusted and propensity score adjusted results will be reported and compared.

Given treated bleeds are event based, a SMRW weighted negative binomial model will be fit to compare ABR between Roctavian and SoC cohort. SMRW will be applied on the SoC cohort to generate a cohort that is more similar to the Roctavian cohort. Other clinically significant prognostic factors or covariates that remain imbalanced after propensity score adjustment will be included in the model as well. Regression coefficients, corresponding 95% CIs and p-values will be reported for all explanatory variables included in the model.

Given some patients may have no treated bleeds based on prior literature,[26] a two-part zero-inflated negative binomial model will also be considered if the negative binomial model does not converge.[27] Akaike Information Criterion (AIC) will be calculated and compared between the models with and without counting for zero-inflation. The model with a lower AIC value will be chosen. For the zero-inflated negative binomial model, first the model will be fit for a binary outcome whether a patient had a treated bleed during the outcome assessment period, and then an ABR count outcome for treated bleeds among patients who had at least one treated bleed during the outcome assessment period (excluding patients with zero bleeds) will be fit. Finally, the unconditional ABR estimates for treated bleed will be calculated by multiplying the estimated conditional ABR from the count model by the probability of having a treated bleed estimated from the binary model for both the Roctavian and SoC cohorts.

7.9.4. Analysis of Secondary Outcomes

The secondary outcomes include other major, life-threatening, and joint ABRs, treatment outcomes, PROs, and safety outcomes. All outcomes will be compared between the Roctavian and SoC cohorts.

7.9.4.1. ABR for Major, Life Threatening, and Joint Bleeds

Population	Measurement Period	Analysis Notes
All patients For interim and analyses at fixed timepoints, only those with specified amounts of follow-up will be included	≥1 year of follow-up, ≥2 years of follow-up, ≥3 years of follow-up, all available follow-up	Patients with no bleeds will be included as having an ABR of 0

As outlined in Section 7.9.3, ABR will also be calculated for major, life threatening, and/or joint bleeding events. For each bleed type, ABR will be calculated by dividing the total number of bleeds in

each cohort with the respective bleed type by the number of days in the reporting window for all patients in that cohort, multiplied by 365.25. ABR of each cohort will be compared over the full follow-up time for each patient in the study, as well as during annual increments during the follow-up period.

Similar to the analytic approach for the primary outcome, an SMRW weighted negative binomial model or a SMRW weighted zero-inflated negative binomial model, whichever appropriate, will be fit to compare each ABR measure between Roctavian and SoC cohorts. SMRW will be applied on the SoC cohort to generate a cohort that is more similar to the Roctavian cohort. Other covariates that remain imbalanced after propensity score adjustment will be included in the model as well. Regression coefficients, corresponding 95% CIs and p-values will be reported for each explanatory variables included in the model.

7.9.4.2. Proportion of Patients with Zero Bleeds

Population	Measurement Period	Analysis Notes
All patients For interim and analyses at fixed timepoints, only those with specified amounts of follow-up will be included	≥1 year of follow-up, ≥2 years of follow-up, ≥3 years of follow-up, all available follow-up	Patients with no bleeds will be included as having an ABR of 0

The proportion of patients who had no bleeding events of each of the following types will be reported and compared between the Roctavian and SoC cohorts: treated bleeds, major bleeds, life threatening bleeds, and joint bleeds. The approach will be generally consistent with the analysis approach for ABRs (see Section 7.9.3) regarding the adjustment approach, analysis of the full follow-up period along with annual increments and start of follow-up period and censoring reasons.

The binary outcomes will be analyzed using propensity score SMRW weighted logistic regression models. The main predictor of interest is the treatment effect (Roctavian vs. SoC), other imbalanced covariates after PS adjustment may be included in the model as necessary. ORs, corresponding 95% CIs and p-values will be reported.

7.9.4.3. Use of Hemostatic Medications

Population	Measurement Period	Analysis Notes
All patients For interim and analyses at fixed timepoints, only those with specified amounts of follow-up will be included	≥1 year of follow-up, ≥2 years of follow-up, ≥3 years of follow-up, all available follow-up	Patients with no treatment will be included as having a treatment value of 0

Cumulative hemostatic medication use will be compared between the Roctavian and the following SoC sub-cohorts:

- FVIII treatment use (IU/kilogram [kg])
- Emicizumab treatment use (milligrams [mg]/kg)

The SoC cohort will be stratified by patients using FVIII treatments and patients using emicizumab. They will separately be compared to the Roctavian cohort. The amount of total (prophylactic and on-demand) treatments utilized per patient per kg (IU/kg or mg/kg; see Table 4) will be calculated across the follow-up period and calculated between the Roctavian, SoC, FVIII, and emicizumab cohorts with the same follow-up measurement approach as the primary ABR outcome (see Section 7.9.3). Due to patient weight not being a required field in the DHR, alternate approaches may be required if IU/kg or mg/kg is not able to be sufficiently calculated; see Section 7.9.5.4 for details. Prophylaxis and on-demand use will be described as available.

The proportion of patients utilizing any hemostatic treatments during follow-up will be described but will not be compared, as 100% of the SoC, FVII, and emicizumab cohorts will utilize hemostatic treatments. The use of FVIII for different reasons recorded in the DHR will also be described for each cohort. For the emicizumab cohort, the number of injections and regimen utilized (if possible, will be described). The proportion of patients utilizing any hemostatic treatments specifically for bleeds or short-term prophylaxis will be compared regarding the absolute difference in the proportion of participants utilizing a Chi-square test. Similar to the analyses of the proportion of patients with zero bleeding, only those participants with follow-up for the full time over which the proportion is calculated will be included in analyses.

The total annual FVIII per kg during follow-up will be compared between the cohorts. Total FVIII per kg for any reason will be compared based on the absolute difference in the mean total FVIII per kg between the Roctavian, SoC, FVIII, and emicizumab cohorts separated by SoC class (PD, SHL, EHL, emicizumab) utilizing a two-sample t-test (two sided). Similar to the analyses of the proportion of patients with zero bleeding, only those participants with follow-up for the full time over which the proportion is calculated will be included in analyses.

Annualized infusion/injection rates (AIRs) will also be compared between the cohorts. AIRs will be calculated for each participant as the number of infusions or injections divided by the time between the start of follow-up and censoring event for the analysis, annualized to the number of infusions/injections in one year. The mean of the individual participant AIRs for each cohort will be calculated and compared. The comparison of AIRs will be based on the absolute difference in the mean AIR between the cohorts utilizing a two-sample t-test (two sided).

For all the outcomes measuring hemostatic medication use described above, both the unweighted and SMRW weighted analyses will be conducted. SMD will be computed to compare the outcomes between cohorts. P-values for each corresponding statistical test will also be reported.

7.9.4.4. Clinical Outcome Assessments

Population	Measurement Period	Analysis Notes
All patients with sufficient follow-up, comparing Roctavian cohort to SoC cohort; Patients without COA scores will not be included	Assessments are expected to be conducted at baseline and every 6 months	Patients are expected to have baseline and at least one follow-up measure

The Hemophilia Joint Health Score (HJHS), Haemo-QoL-A, and Brief Pain Inventory – short form (BPI-sf) will be used to measure COAs. As these instruments standardize collection of data for areas that are monitored in routine clinical practice, the assessments are expected to follow routine clinical follow-up, which typically occurs twice annually for patients. Physicians participating in the AbD are expected to enter data for these instruments collected relative to the study index date (e.g., around the index date and approximately every six months for three years relative to the index date).

7.9.4.4.1. Joint Function

The HJHS is a validated outcome tool developed for the assessment of joint health in people with hemophilia.[28] HJHS measures joint health in the domain of body structure and function (i.e., impairment) of the six joints most commonly affected by bleeding in hemophilia: the left and right knees, left and right ankles, and left and right elbows. It also measures the patient's global gait score. Scores range from 0 to 124 points. This physical examination assessment tool conducted by a healthcare provider is sensitive enough to pick up the subtle early signs of joint damage and is appropriate for monitoring joint change over time or assessing efficacy of treatment regimens among patients receiving both prophylactic and on-demand therapy.[29] Scores within each of the six joint categories will be summed, if not already summed in the DHR. The summed joint scores and the global gait score are expected to be captured at baseline, and at each follow-up time point (every 6 months for approximately 3 years). Patients who have a baseline and at least one follow-up measure for HJHS outcomes will be included in the analysis. To determine the completeness rate, the number of patients in each cohort with a recorded HJHS score (joint scores and/or global gait score) at a given timepoint will be divided by the total number of patients eligible within that cohort (i.e., have enough follow-up time). More specifically, a minimum and full compliance rate will also be calculated. The minimum completion rate is defined as the number of patients who have the baseline measure and at least one post-baseline measure, divided by the total number of enrolled patients. The full completion rate is defined as number of patients who have the baseline measure and all post-baseline measures, divided by the total number of enrolled patients.

Descriptive statistics (mean, SD, median, IQR, minimum, maximum) will be used to summarize the COA scores at baseline, follow-up, and change from baseline. Two-sided t-tests will be used to compare the absolute change in scores from baseline between Roctavian and SoC cohorts. Distribution of the outcome variables will be checked to make sure the assumptions of the two-sided t-test are met. If a skewed distribution is observed, a non-parametric Wilcoxon signed-rank test will be performed instead. SMD of the scores at baseline, follow-up, and change from baseline between the Roctavian and SoC cohorts will also be estimated.[30] SMD values will be classified into small, medium, large or very large based on the following ranges, 0.2-0.5, 0.5-0.8, 0.8, and ≥1.3.

Patients with an evaluable baseline score and at least one evaluable post-baseline score will be included in the change from baseline analyses. Since patients are expected to have a follow-up visit every 6 months, it is expected that COAs will be measured with a maximum of seven time points, baseline, 6±3, 12±3, 18±3, 24±3, 30±3, and 36±3 months. The last follow-up measure will be used in the change from baseline analysis. Based on observed data, the last follow-up measure may be required to have occurred at least a certain number of years after baseline to increase interpretability of results. A general linear mixed model with unstructured covariances will be fit to conduct a longitudinal analysis for each COA outcome. The mixed model is chosen to account for the repeated measures, while allowing flexibility for any potential missing values. No missing data will be imputed.

The explanatory variables that will be included in the model are treatment (Roctavian vs. SoC) and time. Treatment by time interaction will also be included in the model to assess whether the treatment effect changes across time. Residual analysis will be conducted to ensure the independent and identically distributed random variables assumptions of the model residuals are met.

For all the joint function outcomes described above, both the unweighted and SMRW weighted analyses will be conducted. SMD will be computed to compare the outcomes between cohorts. P-values for each corresponding statistical test will also be reported.

7.9.4.4.2. Haemo-QoL-A Score

The Haemo-QoL-A questionnaire is a validated hemophilia-specific health-related quality of life questionnaire for adults.[31] It consists of 41 questions covering six domains (physical functioning, role functioning, worry, consequences of bleeding, emotional impact, and treatment concerns). Items are answered by patients on a 6-point Likert scale, ranging from 0 (none of the time) to 5 (all of the time). Higher scores indicate better health related QoL or less impairment for that particular measure. See Annex 12.2 for the scoring guide. Transformed scores will be calculated for each domain by summing the individual item scores for each domain (actual raw total score), dividing it by the possible raw score range, and then transforming to a standardized scale ranging from 0-100.[32] The formula for the transformed scale is shown below:

$$Transformed\ score = \frac{actual\ raw\ total\ score}{possible\ raw\ score\ range} \times 100$$

Scores for each of the six domains and for the total score are expected to be captured at baseline, and at each follow-up time point (every 6 months for approximately 3 years). Patients who have a baseline and at least one follow-up measure for Haemo-QoL-A outcomes will be included in the analysis. To determine the completeness rate, the number of patients in each cohort with a recorded Haemo-QoL-A score (six domains and/or total score) at a given timepoint will be divided by the total number of patients eligible within that cohort (i.e., have enough follow-up time). More specifically, a minimum and full compliance rate will also be calculated. The minimum completion rate is defined as the number of patients who have the baseline measure and at least one post-baseline measure, divided by the total number of enrolled patients. The full completion rate is defined as number of patients who have the baseline measure and all post-baseline measures, divided by the total number of enrolled patients.

The same analytical techniques to those described above for joint function will be applied to the Haemo-QoL-A outcomes including descriptive statistics, change from baseline analyses and repeated measures model analyses. Please refer to Section 7.9.4.4.1 for details.

7.9.4.4.3. Pain Score

The BPI-sf is a is a validated and frequently used patient-reported questionnaire that assesses pain severity and the impact of pain on daily functions (i.e., pain interference).[33] The BPI-SF measures generic pain (i.e., is not indication-specific) has been used and validated in hemophilia.[34-36]

Four questions measure pain intensity (worst pain, least pain, average pain, and pain now). The pain intensity items use an 11-point numerical scale with zero signifying ("no pain") and 10 signifying ("pain as bad as you can imagine"). The pain interference scale assesses the degree to which pain interferes with 7 constructs (General activity, Mood, Walking ability, Normal work, Relation with people, Sleep, and Enjoyment of life). The pain interference items use an 11-point numerical scale with zero signifying "does not interfere" and 10 signifying "completely interferes." Both the pain intensity and pain interference items have a recall period of the “last/past 24 hours”. Four other items allow patients to report on the nature of their pain.”. Scores are expected to be reported for pain intensity and pain interference at baseline, and at each follow-up time point (every 6 months for

approximately 3 years). Patients who have a baseline and at least one follow-up measure for BPI-sf outcomes will be included in the analysis. To determine the completeness rate, the number of patients in each cohort with a recorded BPI-sf score (average pain and/or pain intensity) at a given timepoint will be divided by the total number of patients eligible within that cohort (i.e., have enough follow-up time). More specifically, a minimum and full compliance rate will also be calculated. The minimum completion rate is defined as the number of patients who have the baseline measure and at least one post-baseline measure, divided by the total number of enrolled patients. The full completion rate is defined as number of patients who have the baseline measure and all post-baseline measures, divided by the total number of enrolled patients.

The same analytical techniques to those described above for joint function will be applied to the Haemo-QoL-A outcomes including descriptive statistics, change from baseline analyses and repeated measures model analyses. Please refer to Section 7.9.4.4.1 for details.

In addition, a responder analysis will be considered for the BPI-sf improvement and deterioration of pain interference and pain intensity scales to understand the magnitude of observed clinically meaningful effects. A responder analysis is defined as an analysis or presentation of the proportion of participants who achieved a pre-defined level of improvement on one of the main outcomes at a certain time point.[37] Based on IQWiG's guidance for responder analysis, (a 15% change of the scale range)[38], patients with a deterioration and improvement (reported separately) in their scores of 15% (e.g., 15% of a 10 point scale is 1.5) from the baseline to the latest follow-up measure will be defined as responders. All other patients will be defined as non-responders. Chi-square tests will be performed as a comparison between the Roctavian and SoC cohorts.

7.9.4.5. Safety Events

Population	Measurement Period	Analysis Notes
All patients	All available follow-up data	Safety events will be compared between the Roctavian and SoC cohorts where there are at least 10 events in each cohort Due to the optional nature of DHR safety event reporting by physician assessment, there is insufficient data to fully describe patient comorbidities that may confound the 'true' causal reason for an event Relevant capture of malignant neoplasms will be dependent on the capture of an 'other relevant event' free text field; not specific to malignant neoplasms

Safety events outlined in Table 5 will be reported for both the Roctavian and SoC cohorts. The proportion, event rate, and incidence rate of each event will be calculated from index through the full follow-up period. Follow-up for safety events will be censored for the analysis based the earliest date after index of withdrawal, loss to follow-up, enrollment of an interventional hemophilia clinical trial, death (inclusive of date of death), end of reporting/follow-up period in the DHR, or end of study follow-up (e.g., index date plus 1,095 days). Patients will similarly be censored analytically, as done in the primary analysis when returning to prophylaxis for the Roctavian cohort or administration of Roctavian in the SoC cohort, though additional descriptive analysis of safety events for these cohorts after the censoring event will be conducted. All patients will be included in analyses of event or incidence rates,

while analyses of the proportion of patients will only include those participants with follow-up for the full time over which the proportion is calculated. See below for the event and incidence rate calculations:

- Event rates will be calculated as the number of events per 100 person-years: (number of events in each cohort during the overall follow-up period / total number of days in each cohort during the follow-up period) * 365.25 * 100. Event rates will be calculated for events that may happen multiple times per person,
- Incidence rate will be calculated as the number of new events (first occurrence of event) per 100 person-years: (number of new events in each cohort during the overall follow-up period / total number of days in each cohort during the follow-up period) * 365.25 * 100. Incidence rates will be calculated for events that can only happen once per person.

Categories of safety events where at least 10 events occur during the follow-up period in both study arms will also be compared between the Roctavian and SoC cohorts in this study.

7.9.4.6. Time to Resumption of Prophylactic Treatment

Population	Measurement Period	Analysis Notes
Roctavian cohort only	All available follow-up data	Definition utilized in this study is relevant to the fields that the DHR collects and will be aligned as best as possible to other definitions utilized external to this study

For patients in the Roctavian cohort, time to resumption of prophylactic treatment will be measured for patients who received SoC prophylaxis after Roctavian administration during the follow-up period. Based on the observed therapy usage data collected in the DHR, the definition of resumption to prophylactic treatment is subject to refinement based on the products used by patients and other treatment aspects as recorded in the DHR data. The current definition of resumption of prophylactic treatment is as follows: three consecutive months of 'prophylaxis' utilizing a threshold for the following treatment types; at least four emicizumab doses, 18 EHL doses, and/or 24 SHL doses. Summary statistics will be utilized to describe time to resumption including mean, SD, median, IQR, minimum, and maximum.

7.9.5. Sub-group and Sensitivity Analysis

Data-driven subgroup and sensitivity analyses are planned. The need for data-driven subgroup and sensitivity analyses will be driven by the number of patients in the Roctavian cohort (for example, if there are few patients, there is likely little need for subgroup/sensitivity analyses) and/or a qualitative assessment (for example, assessment of patient characteristics). If needed, these proposed secondary subgroup and sensitivity analyses will provide another dimension to the study and will add to the robustness of the overall interpretation of study findings.

7.9.5.1. Subgroup Analyses

Subgroup analysis will be performed by taking the full weighted cohort, breaking the matches (if applicable), and then presenting the results for each subgroup. Wang et al compared the performance of this subgroup analysis strategy with other strategies (e.g., using subgroup-specific propensity scores to match within each subgroup) and found none of the five strategies compared were clearly superior to the other in terms of balance, bias, or precision.[39] The selected strategy results in only a

single matched cohort for the full sample even for multiple subgroup analyses. Baseline characteristics and all primary and secondary outcomes will be reported (using the same analytic methods as described above) for the following subgroups of patients:

SoC cohort prophylaxis treatment type

- Patients within the SoC cohort will be stratified based on the prophylaxis treatment received at study consent: emicizumab (alone or in combination with another prophylaxis product), SHL products, EHL products, or PD products. See Table 4 for products that fall within each product type.
- Note, the treatment a patient receives at study consent will only be captured in this analysis, any treatment switch after consent will not be captured by this subgroup analysis.
- Each prophylaxis-specific subgroup will be described and compared to the Roctavian cohort separately as sample size permits.

AAV5 antibody status

- The study results will be stratified by patients with known AAV5 antibody status at study consent (presence) versus those with no known AAV5 antibody status (absence).
- Missing AAV5 status will be categorized as absence. See Table 3 for operationalization of the AAV5 variable.
- Note, the ability to conduct this subgroup analysis is dependent upon the availability of the AAV5 variable in the DHR

7.9.5.2. PSM Sensitivity Analyses

If sample size allows, a sensitivity analysis using PSM with up to a 1:5 ratio of Roctavian and SoC patients is planned. This sensitivity analysis will assess the robustness of the SMRW primary analysis for the primary objective (ABR for treated bleeds) and provide support for the choice of propensity score methods. Sensitivity analyses will be conducted for the secondary objectives only if there is a clinically meaningful difference (e.g., magnitude greater than 2) or a change in directionality of the association in the primary outcome results.

7.9.5.3. Other Sensitivity Analyses

Traumatic Bleeds Sensitivity Analysis

If >10% of the population experiences traumatic bleeds as indicated in the DHR (occasion = “traumatic hemorrhage”), a sensitivity analysis will be conducted to compare the ABRs of those with traumatic bleeds as compared to the overall cohorts (occasion = “suspected hemorrhage”, “spontaneous hemorrhage”, or “hemorrhage, cause unknown”).

Switching Sensitivity Analyses

If >15% of the SoC cohort switches classes of treatment (SHL, EHL, PD, emicizumab) during the follow-up period or if a specific class switching pattern occurs in >10% of the population, a sensitivity analysis will be conducted of patients who remain on the same class for the duration of the follow-up period. ABRs will be calculated for this population that do not switch FVIII classes to understand how this differs from the ABRs for the overall SoC cohort.

COA measures (as described in Section 7.9.4.4) will be described for patients in the SoC cohort who stay on the same class of treatment throughout the duration of the follow-up period.

7.9.5.4. Missing Data Analyses

Data completeness will be evaluated and the proportion of missingness will be reported for inclusion and exclusion criteria, exposure variables, covariate variables, and outcome variables. Data missingness will be described and compared across cohorts. Baseline characteristics in patients with and without missing data will be compared among patients with complete data versus those with any missing data. Missing data will not be imputed unless otherwise stated.

Data Handling Convention for Missing or Partial Dates

The following rules will be used for the imputation and processing of missing or partial dates:

- If day is missing and month and year are populated, the day will be set to 15.
- If month and day are missing and year is populated, the month and day will be set to ‘July 1’.
- If year, month, and day are missing, no date will be imputed.

Methods used to assess missing data will be data driven and finalized based on the available data. Approaches will be tailored based on the specific variables with missing data. Examples of possible approaches include:

- Safety events with missing or partial dates will have dates imputed based on the rules above.

- Participation in a clinical trial is an optional field in the DHR and will be used as an exclusion criterion. If patients do not have data for this field, they will not be included in the study population, as it cannot be confirmed that they fit the study population criteria. No imputation will be used.

- Some baseline variables including comorbidities and family history of hemophilia are optional fields in the DHR. For patients with missing data for these variables, they will be classified as “unknown” in the descriptive reporting.

- Patient weight (kg) is an optional data field that will be used in the outcome analysis of hemostatic medications. If a patient is missing a weight value(s), the nearest weight within 12 months before and after the missing weight value will be used. If weight is missing for <30% of the patient population, the mode weight of the patient population will be imputed for patients with missing values. Further considerations for missing weight values will be explored if >30% of the patient population does not have a weight value recorded.

- COAs will rely on optional fields in the DHR. If patients do not have data for any of the COAs measured in the outcome analysis, they will not be included in the analysis of that particular COA. No imputation will be used.

Any other variables that are optional fields captured by the DHR will be assessed using similar missing data methods. Missing data analyses will be finalized based on data availability and reported in the final study report.

Multiple imputation will be used to impute the values of missing predictors used in the propensity score model to analyze the results, including averaging the propensity score across imputations. Missing values for covariates will be imputed using multiple imputation with 100 imputations before deriving the propensity score model. The fully conditional specification method (multiple imputation using chained equations method) will be used with the discriminant function method used for categorical variables. Continuous variables will be imputed using ordinary linear regression, ordinal variables using ordinal logistic regression, and binary variables using logistic regression.

7.9.5.5. Quantitative Bias Analysis

A quantitative bias assessment will be initiated as a sensitivity analysis to estimate the magnitude and direction of uncertainty resulting from sources of systematic error in this study, particularly for unmeasured confounding nullifying any significant result will be performed.[40] The E-value is the minimum strength of association on the risk ratio (RR) scale that an unmeasured confounder would need to have with both, the outcome and treatment, to wholly explain a particular treatment-outcome association, conditional on measured covariates.

Assuming the effect estimate is > 1, the E-value is calculated as:

E-value = RR + sqrt(RR*(RR-1))

7.9.6. Interim Analysis

Interim results will be reported at six months, 18 months, 36 months, and 54 months after study initiation. Each interim analysis will include the following results:

The initial interim analysis at six months will serve as a status check to describe the number of patients enrolled in the Roctavian and SoC cohorts, the amount of follow-up time for patients enrolled in the respective cohorts, an assessment of study enrollment relative to the proposed sample size, and an assessment to quantify the missingness for each of the endpoint variables.

At the 18-month interim analysis, the Roctavian and SoC cohorts will be described, the propensity score's will be built and assessed for performance, and all outcome analyses will be descriptively reported. Among patients that have at least one year of follow-up, comparative analyses will be performed. The 6-month and 18-month interim analyses will also evaluate the number of enrolled patients who withdraw consent from the study or are otherwise censored.

The 36- and 54-month interim analyses will include all comparative analysis results, although follow-up times will be variable among included patients.

7.9.6.1. Futility Analysis

A futility analysis will be conducted at the 6-month and 18-month interim analyses to assess whether the study should be terminated early due to the inability to meet the required sample size for comparative analyses. The futility analysis will examine the total number of patients enrolled in the study, the number of patients in each of the SoC and Roctavian cohorts, the amount of time remaining in the study selection window, and the numbers of variables available for analysis. Assessments of potential futility and implications on study interpretation will be discussed in the reports associated with these interim analyses. Continued conduct of the study based on the futility assessment at these timepoints will be discussed with the G-BA.

A futility analysis will also be included as part of the 36-month and 54-month interim analyses to determine the observed ABR of each cohort. Implications on study interpretation will be discussed in

the reports associated with these interim analyses. Continued conduct of the study based on the futility assessment at these timepoints will be discussed with the G-BA.

7.9.7. Implausible Data and Outliers

Given the data may be skewed, outliers will be checked by boxplot. IQR is defined as the difference between the 3rd and 1st quartile. Observations that are below (Q1 – 1.5 x IQR) or above (Q3 + 1.5 × IQR) will be evaluated (except for bleed counts which may have excess zeros). Also, individual data points that do not align with biologically or clinically plausible values (e.g., patient weight <10 kg, patient with >100 bleeds per year) will be reviewed and removed if determined to be implausible. For linear regression models, residual analysis will be conducted and Cook's distance will be computed to measure the influence of individual data points.[41]

7.10. Limitations of the Statistical Analysis

This study has several limitations inherent to the observational nature of the study and use of registry data.

- **Selection bias**: Selection bias is a distortion of evidence or data that arises from the way that the data are collected. Patients eligible for, and who consent to participate in, this study may not be representative of the overall population of PwSHA in Germany, limiting the generalizability of findings from that data.
- **Confounding bias**: Confounding bias occurs when the effects of a treatment or the exposition effect of the disease vary by the presence/level of another factor (effect modifier). Due to the absence of patient randomization, Roctavian and SoC therapies may be prescribed to groups of patients with prognostic differences, thus limiting generalizability of results. The analytic approach of using propensity scores aims to account for these differences. The study team will exercise flexibility in the propensity score weighting scheme to ensure optimal balance between the exposed and unexposed populations indexed. However, unobserved/unmeasured confounding may still be present. To account for possible unmeasured confounding, a quantitative bias assessment will be performed.
- **Loss to follow-up**: Patient retention through the end of the expected observation period will be monitored carefully and attempts will be made to obtain follow-up data from patients who discontinue treatment. However, some patients may have fewer than three years of follow-up data available. Patients in the SoC cohort are expected to have follow-up twice per year whereas patients in the Roctavian cohort may have more frequent touchpoints due to them being on a newer treatment.
- **Missing data**: The data leveraged for this study are dependent on physicians and hospitals to accurately record each event. Methods are in place for handling missing data (Section 9.7.5) and a sensitivity analysis of missing data will be conducted.
- **Heterogeneity of SoC**: The assumption of treatment consistency specifies that there is no ambiguity defining a treatment. This assumption is also known by the term "treatment variation irrelevance". For this study, the two compared treatment groups are Roctavian versus SoC with SoC being different for various patients. Therefore, treatment consistency is approximately met if these different SoC treatments are considered to result in approximately equal treatment effects. As outlined in Section 7.4.2, SoC prophylaxis treatment types were assumed to have similar efficacy, QoL, and safety profiles, and therefore, are pooled together as 1 SoC control cohort. While there is minimal evidence that prophylactic SoC treatments are largely heterogeneous regarding efficacy, QoL and safety profiles, a sensitivity analysis will be performed to analyze the SoC treatment types separately, as outlined in Section 7.9.5.2, and results may be reported for each SoC treatment separately if necessary.

- **Measurement error**: Measurement error is the difference between a measured quantity and its true value. Data in the DHR are collected for more general purposes (not specifically for this study), therefore, some medical information not directly related to this study may be incomplete or not available at all. The consistency of the available information may vary across study years since the data are entered by physicians based on general patient follow-up. This can affect the measurement of exposure to SoC treatments, the outcomes of interest and/or the covariates. To ensure that the accuracy of the retrieved information is acceptable, all data will be reviewed for possible inconsistencies or implausible information.

7.11. Quality Control

All aspects of the study will be conducted within the framework of the [redacted] Quality Management System. A Quality Control (QC) checklist for the study will be developed and executed, which will include QC on the study SAP. Furthermore:

- The study QC checklist will establish ownership for the execution of the individual QC steps
- The Principal in Charge of the study project will ensure that individuals responsible for the execution of specific QC steps will have the knowledge, capability, and experience necessary to perform the assigned tasks
- The result of the execution of the individual steps of the QC plan will be documented, and will include the required corrective actions, if any. The execution of any required corrective action will also be documented.

The QC checklist will be subjected to a final review and approval for sufficiency and completeness from the Principal in Charge.

[redacted] is responsible for the quality of the data provided to BioMarin or its designee for analysis. The Advanced Analytics team will employ a two-programmer approach to ensure accuracy and reproducibility of coding, including a multi-point QC checklist for retrospective database studies and independent double-programming of analyses. Programming code and QC plans/output are to be made available to BioMarin.

7.11.1. [redacted] Quality Management System

At the study level, all aspects of the study from protocol development to the reporting of the results are conducted within the work-frame of [redacted] Quality Management System and in accordance with the global procedure [redacted].

A QC checklist will be developed and executed for the study, which will include quality control on study methodology, statistical analysis plan, programming, data management and analysis, study results, conclusions, and study report. Furthermore:

- The study QC checklist will establish ownership for the execution of the individual QC steps. The principle of the independence of QC applies
- Individuals responsible for the execution of specific QC steps must have knowledge, capability and experience which are adequate for the task.
- The result of the execution of the individual steps of the QC checklist will be documented, and include the required corrective actions, if any.
- The execution of any required corrective action will be documented.

Also, [redacted] employees contributing to the study must be trained, as per [redacted] procedure [redacted].

8. Protection of Human Subjects Related to the Analysis

Measures will be taken to ensure the privacy of subject data in accordance with the principals of the DHR. [redacted] will follow all applicable regulations and guidelines in the relevant locality, country, and/or region to protect the privacy of subject data. The study is conducted in accordance with the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) Code of Conduct,[42] the International Society for Pharmacoepidemiology Guidelines for Good Pharmacoepidemiology Practices (GPP),[43] the Declaration of Helsinki and Council for International Organizations of Medical Sciences International Ethical Guidelines its amendments, and any applicable national guidelines, laws and regulations. BioMarin, [redacted] other participating entities and individuals acting on their behalf commit to adhere to the rules of the ENCePP Code of Conduct in their entirety.

9. Management and Reporting of Adverse Events/ Adverse Drug Reactions

Secondary use of data in observational research means that there is no potential to collect individual serious and non-serious adverse events (AEs), pregnancy exposures, or incidents related to BioMarin products during the conduct of this research as the minimum criteria needed to report AEs, pregnancy exposures, and incidents are not present in the data source.

Therefore, the reporting of adverse drug reactions (ADRs) in the form of individual case safety reports will not be performed for data extracted from the DHR (GVP VI.C.1.2.1.b). It is assumed that reporting of corresponding safety data extracted/analyzed as part of this study has been appropriately performed in accordance with local requirements and documented at the time these data were collected through primary data collection mechanisms. On-site monitoring study monitoring visits as described in the protocol will be utilized to ensure that relevant adverse events are reported are reported to the study sponsor for participants in this study consistent with local practice.

In Germany physicians are obliged to report unintended drug reactions (unerwünschte Arzneimittelwirkungen) coming to their attention in the context of their therapeutic activity to the Drug Commission of the German Medical Profession (Arzneimittelkommission der deutschen Ärzteschaft, specialist committee of the German Medical Association) and incidents relating to the use of medical devices to the relevant competent authority.[44]

Safety data addressing the objectives of the study will be summarized in each interim report and in the final study report.

10. Plans for Disseminating and Communicating Study Results

BioMarin recognizes the importance of communicating medical study data and therefore encourages the publication of these data in reputable, peer-reviewed scientific journals and at seminars or conferences. Consideration for authorship of each publication will be based on the authorship criteria defined in the Uniform Requirements for Manuscripts Submitted to Biomedical Journals ("Uniform Requirements") of the International Committee of Medical Journal Editors (http://www.icmje.org/ethical_1author.html) and publication development will proceed in alignment with Good Publication Practice for Communicating Company Sponsored Medical Research (https://www.acpjournals.org/doi/10.7326/M15-0288).

The posting of study information and study results will comply with applicable national regulatory requirements and BioMarin's data sharing policy available at https://www.biomarin.com/data-request-form/.

11. References

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12. Annexes

12.1. Table Shells

Table 1 Sample Attrition for Roctavian and SoC Cohorts

		Roctavian Cohort				SoC Cohort			
Step #	Attrition steps (to be applied sequentially)	Excluded		Remaining		Excluded		Remaining	
		N	%	N	%	N	%	N	%
1	Male PwSHA as recorded in the DHR			0	0.00%			0	0.00%
2	≥18 years of age at index	0	0.00%	0	0.00%	0	0.00%	0	0.00%
3	Treated with Roctavian or SoC hemostatic prophylaxis:								
	a) Commercially available Roctavian (Roctavian cohort)	0	0.00%	0	0.00%				
	b) Prophylactic treatment with FVIII or emicizumab for ≥12 months prior to study entry (SoC cohort)					0	0.00%	0	0.00%
4	Not currently in, or previously participated (in the last 12 months before index), an interventional clinical trial involving an investigational product to treat HA	0	0.00%	0	0.00%	0	0.00%	0	0.00%
5	With no history of inhibitors against FVIII ever (or current) as recorded in the DHR prior to index	0	0.00%	0	0.00%	0	0.00%	0	0.00%
	Final cohorts			0				0	

Data source: DHR from Q1 2023 to Q3 2028
Acronyms: DHR: Deutsches Hämophilieregister; SoC: standard of care; PwSHA: people with severe hemophilia A; FVIII: coagulation factor VIII; HA: hemophilia A

Table 2 Baseline and Demographic Characteristics for Roctavian and SoC Cohorts

Measures	Unadjusted						After SMRW					
	Roctavian Cohort N=		SoC Cohort N=		p-value (Roctavian vs. SoC)	Std. Diff. (Roctavian vs. SoC)	Roctavian Cohort N=		SoC Cohort N=		p-value (Roctavian vs. SoC)	Std. Diff. (Roctavian vs. SoC)
	N	(%)	N	(%)			N	(%)	N	(%)		
Age (years)												
Mean	0.00		0.00		0.0000	0.00	0.00		0.00		0.0000	0.00
SD	0.00		0.00				0.00		0.00			
Median	0		0		0.0000		0		0		0.0000	
Q1	0		0				0		0			
Q3	0		0				0		0			
Min	0		0				0		0			
Max	0		0				0		0			
Age categories (years)												
18-40	0	0.0%	0	0.0%	0.0000	0.00	0	0.0%	0	0.0%	0.0000	0.00
41-64	0	0.0%	0	0.0%			0	0.0%	0	0.0%		
≥65	0	0.0%	0	0.0%			0	0.0%	0	0.0%		
18-23	0	0.0%	0	0.0%	0.0000	0.00	0	0.0%	0	0.0%	0.0000	0.00
24-29	0	0.0%	0	0.0%			0	0.0%	0	0.0%		
30-35	0	0.0%	0	0.0%			0	0.0%	0	0.0%		
36-41	0	0.0%	0	0.0%			0	0.0%	0	0.0%		
42-47	0	0.0%	0	0.0%			0	0.0%	0	0.0%		
48-53	0	0.0%	0	0.0%			0	0.0%	0	0.0%		
54-59	0	0.0%	0	0.0%			0	0.0%	0	0.0%		
60-65	0	0.0%	0	0.0%			0	0.0%	0	0.0%		
66-71	0	0.0%	0	0.0%			0	0.0%	0	0.0%		
72-77	0	0.0%	0	0.0%			0	0.0%	0	0.0%		
78-83	0	0.0%	0	0.0%			0	0.0%	0	0.0%		
84-89	0	0.0%	0	0.0%			0	0.0%	0	0.0%		
≥90	0	0.0%	0	0.0%			0	0.0%	0	0.0%		
Age at first HA diagnosis (years)												
Mean	0.00		0.00		0.0000	0.00	0.00		0.00		0.0000	0.00
SD	0.00		0.00				0.00		0.00			

Measures	Unadjusted						After SMRW					
	Roctavian Cohort N=		SoC Cohort N=		p-value (Roctavian vs. SoC)	Std. Diff. (Roctavian vs. SoC)	Roctavian Cohort N=		SoC Cohort N=		p-value (Roctavian vs. SoC)	Std. Diff. (Roctavian vs. SoC)
	N	(%)	N	(%)			N	(%)	N	(%)		
Median	0		0		0.0000		0		0		0.0000	
Q1	0		0				0		0			
Q3	0		0				0		0			
Min	0		0				0		0			
Max	0		0				0		0			
Age at first FVIII administration (years)												
Mean	0.00		0.00		0.0000	0.00	0.00		0.00		0.0000	0.00
SD	0.00		0.00				0.00		0.00			
Median	0		0		0.0000		0		0		0.0000	
Q1	0		0				0		0			
Q3	0		0				0		0			
Min	0		0				0		0			
Max	0		0				0		0			
Family history of hemophilia												
Yes	0	0.0%	0	0.0%	0.0000	0.00	0	0.0%	0	0.0%	0.0000	0.00
No	0	0.0%	0	0.0%			0	0.0%	0	0.0%		
Unknown	0	0.0%	0	0.0%			0	0.0%	0	0.0%		
HTC (to be finalized upon review of the data)												
A	0	0.0%	0	0.0%	0.0000	0.00	0	0.0%	0	0.0%	0.0000	0.00
B	0	0.0%	0	0.0%			0	0.0%	0	0.0%		
C	0	0.0%	0	0.0%			0	0.0%	0	0.0%		

Data source: DHR from Q1 2023 to Q3 2028
Acronyms: SoC: standard of care; SD: standard deviation; FVIII: coagulation factor VIII; HA: hemophilia A; HTC: hemophilia treatment center
Note: Variable categories will be finalized upon review of the data.
Note: Std. diff. examines the balance of covariate distribution between groups, with a value >0.1 indicating some imbalance between groups and >0.25 indicating poor balance.

Table 3 Baseline Clinical Characteristics for Roctavian and SoC Cohorts

Measures	Unadjusted						After SMRW					
	Roctavian Cohort N=		SoC Cohort N=		p-value (Roctavian vs. SoC)	Std. Diff. (Roctavian vs. SoC)	Roctavian Cohort N=		SoC Cohort N=		p-value (Roctavian vs. SoC)	Std. Diff. (Roctavian vs. SoC)
	N	(%)	N	(%)			N	(%)	N	(%)		
Height (cm)												
Mean	0.00		0.00		0.0000	0.00	0.00		0.00		0.0000	0.00
SD	0.00		0.00				0.00		0.00			
Median	0		0		0.0000		0		0		0.0000	
Q1	0		0				0		0			
Q3	0		0				0		0			
Min	0		0				0		0			
Max	0		0				0		0			
Weight (kg)												
Mean	0.00		0.00		0.0000	0.00	0.00		0.00		0.0000	0.00
SD	0.00		0.00				0.00		0.00			
Median	0		0		0.0000		0		0		0.0000	
Q1	0		0				0		0			
Q3	0		0				0		0			
Min	0		0				0		0			
Max	0		0				0		0			
BMI												
<18.50	0	0.0%	0	0.0%	0.0000	0.00	0	0.0%	0	0.0%	0.0000	0.00
18.50 - <25.00	0	0.0%	0	0.0%			0	0.0%	0	0.0%		
25.00 - <30.00	0	0.0%	0	0.0%			0	0.0%	0	0.0%		
≥30.00	0	0.0%	0	0.0%			0	0.0%	0	0.0%		
HCV infection												
No infection	0	0.0%	0	0.0%	0.0000	0.00	0	0.0%	0	0.0%	0.0000	0.00
Active and/or cured infection	0	0.0%	0	0.0%			0	0.0%	0	0.0%		
Unknown	0	0.0%	0	0.0%			0	0.0%	0	0.0%		
Chronic liver disease												
Liver fibrosis	0	0.0%	0	0.0%	0.0000	0.00	0	0.0%	0	0.0%	0.0000	0.00

Measures	Unadjusted						After SMRW					
	Roctavian Cohort N=		SoC Cohort N=		p-value (Roctavian vs. SoC)	Std. Diff. (Roctavian vs. SoC)	Roctavian Cohort N=		SoC Cohort N=		p-value (Roctavian vs. SoC)	Std. Diff. (Roctavian vs. SoC)
	N	(%)	N	(%)			N	(%)	N	(%)		
Liver cirrhosis	0	0.0%	0	0.0%			0	0.0%	0	0.0%		
Not specified/ unknown	0	0.0%	0	0.0%			0	0.0%	0	0.0%		
Other comorbidities (to be finalized upon review of the data)												
Comorbidity 1	0	0.0%	0	0.0%	0.0000	0.00	0	0.0%	0	0.0%	0.0000	0.00
Comorbidity 2	0	0.0%	0	0.0%			0	0.0%	0	0.0%		
Comorbidity 3	0	0.0%	0	0.0%			0	0.0%	0	0.0%		
Comorbidity 4	0	0.0%	0	0.0%			0	0.0%	0	0.0%		
Target joints												
Yes	0	0.0%	0	0.0%	0.0000	0.00	0	0.0%	0	0.0%	0.0000	0.00
No	0	0.0%	0	0.0%			0	0.0%	0	0.0%		
Unknown	0	0.0%	0	0.0%			0	0.0%	0	0.0%		
Number of target joints												
Mean	0.00		0.00		0.0000	0.00	0.00		0.00		0.0000	0.00
SD	0.00		0.00				0.00		0.00			
Median	0		0		0.0000		0		0		0.0000	
Q1	0		0				0		0			
Q3	0		0				0		0			
Min	0		0				0		0			
Max	0		0				0		0			
Prophylaxis type												
FVIII only	0	0.0%	0	0.0%	0.0000	0.00	0	0.0%	0	0.0%	0.0000	0.00
Emicizumab	0	0.0%	0	0.0%			0	0.0%	0	0.0%		
Any SoC prophylaxis	0	0.0%	0	0.0%			0	0.0%	0	0.0%		
AAV5 antibody status												
AAV5 Tab-	0	0.0%					0	0.0%				

Measures	Unadjusted						After SMRW					
	Roctavian Cohort N=		SoC Cohort N=		p-value (Roctavian vs. SoC)	Std. Diff. (Roctavian vs. SoC)	Roctavian Cohort N=		SoC Cohort N=		p-value (Roctavian vs. SoC)	Std. Diff. (Roctavian vs. SoC)
	N	(%)	N	(%)			N	(%)	N	(%)		
AAV5 Tab+	0	0.0%					0	0.0%				
Use of immunosuppression												
Yes	0	0.0%					0	0.0%				
No	0	0.0%					0	0.0%				
FVIII infusion rate (number of infusions/year), SHL												
Mean	0.00		0.00		0.0000	0.00	0.00		0.00		0.0000	0.00
SD	0.00		0.00				0.00		0.00			
Median	0		0		0.0000		0		0		0.0000	
Q1	0		0				0		0			
Q3	0		0				0		0			
Min	0		0				0		0			
Max	0		0				0		0			
FVIII infusion rate (number of infusions/year), EHL												
Mean	0.00		0.00		0.0000	0.00	0.00		0.00		0.0000	0.00
SD	0.00		0.00				0.00		0.00			
Median	0		0		0.0000		0		0		0.0000	
Q1	0		0				0		0			
Q3	0		0				0		0			
Min	0		0				0		0			
Max	0		0				0		0			
FVIII infusion rate (number of infusions/year), PD												
Mean	0.00		0.00		0.0000	0.00	0.00		0.00		0.0000	0.00
SD	0.00		0.00				0.00		0.00			
Median	0		0		0.0000		0		0		0.0000	

Measures	Unadjusted						After SMRW					
	Roctavian Cohort N=		SoC Cohort N=		p-value (Roctavian vs. SoC)	Std. Diff. (Roctavian vs. SoC)	Roctavian Cohort N=		SoC Cohort N=		p-value (Roctavian vs. SoC)	Std. Diff. (Roctavian vs. SoC)
	N	(%)	N	(%)			N	(%)	N	(%)		
Q1	0		0				0		0			
Q3	0		0				0		0			
Min	0		0				0		0			
Max	0		0				0		0			
FVIII infusion rate (number of infusions/year), emicizumab												
Mean	0.00		0.00		0.0000	0.00	0.00		0.00		0.0000	0.00
SD	0.00		0.00				0.00		0.00			
Median	0		0		0.0000		0		0		0.0000	
Q1	0		0				0		0			
Q3	0		0				0		0			
Min	0		0				0		0			
Max	0		0				0		0			
Annualized baseline FVIII utilization (IU/kg/year), bleeds												
Mean	0.00		0.00		0.0000	0.00	0.00		0.00		0.0000	0.00
SD	0.00		0.00				0.00		0.00			
Median	0		0		0.0000		0		0		0.0000	
Q1	0		0				0		0			
Q3	0		0				0		0			
Min	0		0				0		0			
Max	0		0				0		0			
Annualized baseline FVIII utilization (IU/kg/year), prophylaxis												
Mean	0.00		0.00		0.0000	0.00	0.00		0.00		0.0000	0.00
SD	0.00		0.00				0.00		0.00			
Median	0		0		0.0000		0		0		0.0000	

Measures	Unadjusted						After SMRW					
	Roctavian Cohort N=		SoC Cohort N=		p-value (Roctavian vs. SoC)	Std. Diff. (Roctavian vs. SoC)	Roctavian Cohort N=		SoC Cohort N=		p-value (Roctavian vs. SoC)	Std. Diff. (Roctavian vs. SoC)
	N	(%)	N	(%)			N	(%)	N	(%)		
Q1	0		0				0		0			
Q3	0		0				0		0			
Min	0		0				0		0			
Max	0		0				0		0			
Annualized baseline FVIII utilization (IU/kg/year), short-term prophylaxis												
Mean	0.00		0.00		0.0000	0.00	0.00		0.00		0.0000	0.00
SD	0.00		0.00				0.00		0.00			
Median	0		0		0.0000		0		0		0.0000	
Q1	0		0				0		0			
Q3	0		0				0		0			
Min	0		0				0		0			
Max	0		0				0		0			
Annualized baseline FVIII utilization (IU/kg/year), surgery												
Mean	0.00		0.00		0.0000	0.00	0.00		0.00		0.0000	0.00
SD	0.00		0.00				0.00		0.00			
Median	0		0		0.0000		0		0		0.0000	
Q1	0		0				0		0			
Q3	0		0				0		0			
Min	0		0				0		0			
Max	0		0				0		0			
Annualized baseline FVIII utilization (IU/kg/year), ITT												
Mean	0.00		0.00		0.0000	0.00	0.00		0.00		0.0000	0.00
SD	0.00		0.00				0.00		0.00			
Median	0		0		0.0000		0		0		0.0000	
Q1	0		0				0		0			
Q3	0		0				0		0			

Measures	Unadjusted						After SMRW					
	Roctavian Cohort N=		SoC Cohort N=		p-value (Roctavian vs. SoC)	Std. Diff. (Roctavian vs. SoC)	Roctavian Cohort N=		SoC Cohort N=		p-value (Roctavian vs. SoC)	Std. Diff. (Roctavian vs. SoC)
	N	(%)	N	(%)			N	(%)	N	(%)		
Min	0		0				0		0			
Max	0		0				0		0			
Annualized baseline FVIII utilization (IU/kg/year), other/unknown reason												
Mean	0.00		0.00		0.0000	0.00	0.00		0.00		0.0000	0.00
SD	0.00		0.00				0.00		0.00			
Median	0		0		0.0000		0		0		0.0000	
Q1	0		0				0		0			
Q3	0		0				0		0			
Min	0		0				0		0			
Max	0		0				0		0			
Baseline ABR, overall												
Mean	0.00		0.00		0.0000	0.00	0.00		0.00		0.0000	0.00
SD	0.00		0.00				0.00		0.00			
Median	0		0		0.0000		0		0		0.0000	
Q1	0		0				0		0			
Q3	0		0				0		0			
Min	0		0				0		0			
Max	0		0				0		0			
Baseline treated ABR												
Mean	0.00		0.00		0.0000	0.00	0.00		0.00		0.0000	0.00
SD	0.00		0.00				0.00		0.00			
Median	0		0		0.0000		0		0		0.0000	
Q1	0		0				0		0			
Q3	0		0				0		0			
Min	0		0				0		0			
Max	0		0				0		0			

Measures	Unadjusted						After SMRW					
	Roctavian Cohort N=		SoC Cohort N=		p-value (Roctavian vs. SoC)	Std. Diff. (Roctavian vs. SoC)	Roctavian Cohort N=		SoC Cohort N=		p-value (Roctavian vs. SoC)	Std. Diff. (Roctavian vs. SoC)
	N	(%)	N	(%)			N	(%)	N	(%)		
Baseline major ABR												
Mean	0.00		0.00		0.0000	0.00	0.00		0.00		0.0000	0.00
SD	0.00		0.00				0.00		0.00			
Median	0		0		0.0000		0		0		0.0000	
Q1	0		0				0		0			
Q3	0		0				0		0			
Min	0		0				0		0			
Max	0		0				0		0			
Baseline life-threatening ABR												
Mean	0.00		0.00		0.0000	0.00	0.00		0.00		0.0000	0.00
SD	0.00		0.00				0.00		0.00			
Median	0		0		0.0000		0		0		0.0000	
Q1	0		0				0		0			
Q3	0		0				0		0			
Min	0		0				0		0			
Max	0		0				0		0			
Baseline joint ABR												
Mean	0.00		0.00		0.0000	0.00	0.00		0.00		0.0000	0.00
SD	0.00		0.00				0.00		0.00			
Median	0		0		0.0000		0		0		0.0000	
Q1	0		0				0		0			
Q3	0		0				0		0			
Min	0		0				0		0			
Max	0		0				0		0			

Data source: DHR from Q1 2023 to Q3 2028
Acronyms: SoC: standard of care; SD: standard deviation; BMI: body mass index; HCV: hepatitis C virus; AAV5: adeno-associated virus type 5; FVIII: coagulation factor VIII; SHL: standard half-life; EHL: extended half-life; PD: plasma-derived; IU: international units; kg: kilogram; ITT: immune tolerant therapy; ABR: annualized bleeding rate
Note: Variable categories will be finalized upon review of the data.
Note: Std. diff. examines the balance of covariate distribution between groups, with a value >0.1 indicating some imbalance between groups and >0.25 indicating poor balance.

Table 4 Logistic Regression Model for Development of Propensity Score (PS)

Measures	Parameter Estimate	Standard Error	95% Confidence Limits		p-value
			Lower Limit	Upper Limit	
Covariate 1	0.00	0.00	0.00	0.00	0.0000
Covariate 2	0.00	0.00	0.00	0.00	0.0000
Covariate 3	0.00	0.00	0.00	0.00	0.0000
Covariate 4	0.00	0.00	0.00	0.00	0.0000
Covariate 5	0.00	0.00	0.00	0.00	0.0000
Covariate 6	0.00	0.00	0.00	0.00	0.0000

Note: Covariates will be finalized upon model development.

Table 5 ABR for Roctavian and SoC Cohorts

Measures	Unadjusted				After SMRW			
	Roctavian Cohort N=	SoC Cohort N=	p-value (Roctavian vs. SoC)	Std. Diff. (Roctavian vs. SoC)	Roctavian Cohort N=	SoC Cohort N=	p-value (Roctavian vs. SoC)	Std. Diff. (Roctavian vs. SoC)
Treated ABR, Overall								
Mean	0.00	0.00	0.0000	0.00	0.00	0.00	0.0000	0.00
SD	0.00	0.00			0.00	0.00		
Median	0	0	0.0000		0	0	0.0000	
Q1	0	0			0	0		
Q3	0	0			0	0		
Min	0	0			0	0		
Max	0	0			0	0		
Treated ABR, ≥1 year follow-up								
Mean	0.00	0.00	0.0000	0.00	0.00	0.00	0.0000	0.00
SD	0.00	0.00			0.00	0.00		
Median	0	0	0.0000		0	0	0.0000	
Q1	0	0			0	0		
Q3	0	0			0	0		
Min	0	0			0	0		
Max	0	0			0	0		
Treated ABR, ≥2 years follow-up								
Mean	0.00	0.00	0.0000	0.00	0.00	0.00	0.0000	0.00
SD	0.00	0.00			0.00	0.00		
Median	0	0	0.0000		0	0	0.0000	
Q1	0	0			0	0		
Q3	0	0			0	0		
Min	0	0			0	0		
Max	0	0			0	0		
Treated ABR, ≥3 years follow-up								
Mean	0.00	0.00	0.0000	0.00	0.00	0.00	0.0000	0.00
SD	0.00	0.00			0.00	0.00		

Measures	Unadjusted				After SMRW			
	Roctavian Cohort N=	SoC Cohort N=	p-value (Roctavian vs. SoC)	Std. Diff. (Roctavian vs. SoC)	Roctavian Cohort N=	SoC Cohort N=	p-value (Roctavian vs. SoC)	Std. Diff. (Roctavian vs. SoC)
Median	0	0	0.0000		0	0	0.0000	
Q1	0	0			0	0		
Q3	0	0			0	0		
Min	0	0			0	0		
Max	0	0			0	0		
Major ABR, Overall								
Mean	0.00	0.00	0.0000	0.00	0.00	0.00	0.0000	0.00
SD	0.00	0.00			0.00	0.00		
Median	0	0	0.0000		0	0	0.0000	
Q1	0	0			0	0		
Q3	0	0			0	0		
Min	0	0			0	0		
Max	0	0			0	0		
Major ABR, ≥1 year follow-up								
Mean	0.00	0.00	0.0000	0.00	0.00	0.00	0.0000	0.00
SD	0.00	0.00			0.00	0.00		
Median	0	0	0.0000		0	0	0.0000	
Q1	0	0			0	0		
Q3	0	0			0	0		
Min	0	0			0	0		
Max	0	0			0	0		
Major ABR, ≥2 years follow-up								
Mean	0.00	0.00	0.0000	0.00	0.00	0.00	0.0000	0.00
SD	0.00	0.00			0.00	0.00		
Median	0	0	0.0000		0	0	0.0000	
Q1	0	0			0	0		
Q3	0	0			0	0		
Min	0	0			0	0		
Max	0	0			0	0		

Measures	Unadjusted				After SMRW			
	Roctavian Cohort N=	SoC Cohort N=	p-value (Roctavian vs. SoC)	Std. Diff. (Roctavian vs. SoC)	Roctavian Cohort N=	SoC Cohort N=	p-value (Roctavian vs. SoC)	Std. Diff. (Roctavian vs. SoC)
Major ABR, ≥3 years follow-up								
Mean	0.00	0.00	0.0000	0.00	0.00	0.00	0.0000	0.00
SD	0.00	0.00			0.00	0.00		
Median	0	0	0.0000		0	0	0.0000	
Q1	0	0			0	0		
Q3	0	0			0	0		
Min	0	0			0	0		
Max	0	0			0	0		
Life-threatening ABR, Overall								
Mean	0.00	0.00	0.0000	0.00	0.00	0.00	0.0000	0.00
SD	0.00	0.00			0.00	0.00		
Median	0	0	0.0000		0	0	0.0000	
Q1	0	0			0	0		
Q3	0	0			0	0		
Min	0	0			0	0		
Max	0	0			0	0		
Life-threatening ABR, ≥1 year follow-up								
Mean	0.00	0.00	0.0000	0.00	0.00	0.00	0.0000	0.00
SD	0.00	0.00			0.00	0.00		
Median	0	0	0.0000		0	0	0.0000	
Q1	0	0			0	0		
Q3	0	0			0	0		
Min	0	0			0	0		
Max	0	0			0	0		
Life-threatening ABR, ≥2 years follow-up								
Mean	0.00	0.00	0.0000	0.00	0.00	0.00	0.0000	0.00
SD	0.00	0.00			0.00	0.00		
Median	0	0	0.0000		0	0	0.0000	
Q1	0	0			0	0		

Measures	Unadjusted				After SMRW			
	Roctavian Cohort N=	SoC Cohort N=	p-value (Roctavian vs. SoC)	Std. Diff. (Roctavian vs. SoC)	Roctavian Cohort N=	SoC Cohort N=	p-value (Roctavian vs. SoC)	Std. Diff. (Roctavian vs. SoC)
Q3	0	0			0	0		
Min	0	0			0	0		
Max	0	0			0	0		
Life-threatening ABR, ≥3 years follow-up								
Mean	0.00	0.00	0.0000	0.00	0.00	0.00	0.0000	0.00
SD	0.00	0.00			0.00	0.00		
Median	0	0	0.0000		0	0	0.0000	
Q1	0	0			0	0		
Q3	0	0			0	0		
Min	0	0			0	0		
Max	0	0			0	0		
Joint ABR, Overall								
Mean	0.00	0.00	0.0000	0.00	0.00	0.00	0.0000	0.00
SD	0.00	0.00			0.00	0.00		
Median	0	0	0.0000		0	0	0.0000	
Q1	0	0			0	0		
Q3	0	0			0	0		
Min	0	0			0	0		
Max	0	0			0	0		
Joint ABR, ≥1 year follow-up								
Mean	0.00	0.00	0.0000	0.00	0.00	0.00	0.0000	0.00
SD	0.00	0.00			0.00	0.00		
Median	0	0	0.0000		0	0	0.0000	
Q1	0	0			0	0		
Q3	0	0			0	0		
Min	0	0			0	0		
Max	0	0			0	0		
Joint ABR, ≥2 years follow-up								
Mean	0.00	0.00	0.0000	0.00	0.00	0.00	0.0000	0.00

Measures	Unadjusted				After SMRW			
	Roctavian Cohort N=	SoC Cohort N=	p-value (Roctavian vs. SoC)	Std. Diff. (Roctavian vs. SoC)	Roctavian Cohort N=	SoC Cohort N=	p-value (Roctavian vs. SoC)	Std. Diff. (Roctavian vs. SoC)
SD	0.00	0.00			0.00	0.00		
Median	0	0	0.0000		0	0	0.0000	
Q1	0	0			0	0		
Q3	0	0			0	0		
Min	0	0			0	0		
Max	0	0			0	0		
Joint ABR, ≥3 years follow-up								
Mean	0.00	0.00	0.0000	0.00	0.00	0.00	0.0000	0.00
SD	0.00	0.00			0.00	0.00		
Median	0	0	0.0000		0	0	0.0000	
Q1	0	0			0	0		
Q3	0	0			0	0		
Min	0	0			0	0		
Max	0	0			0	0		

Data source: DHR from Q1 2023 to Q3 2028
Acronyms: ABR: annualized bleeding rate; SoC: standard of care; SD: standard deviation
Note: Std. diff. examines the balance of covariate distribution between groups, with a value >0.1 indicating some imbalance between groups and >0.25 indicating poor balance.

Table 6 SMRW-Adjusted Negative Binomial Regression Model of ABR for the Overall Timeframe, Roctavian and SoC Cohorts

Unadjusted Negative Binomial Regression Model

Measures	Regression coefficient	95% Confidence Limits		r^2	p-value
		Lower Limit	Upper Limit		
Treated bleeds					
Roctavian (vs. SoC)	0.00	0.00	0.00	0.00	0.0000
Major bleeds					
Roctavian (vs. SoC)	0.00	0.00	0.00	0.00	0.0000
Life-threatening bleeds					
Roctavian (vs. SoC)	0.00	0.00	0.00	0.00	0.0000
Joint bleeds					
Roctavian (vs. SoC)	0.00	0.00	0.00	0.00	0.0000

Adjusted Negative Binomial Regression Model (if conducted)

Measures	Regression coefficient	95% Confidence Limits		r^2	p-value
		Lower Limit	Upper Limit		
Treated bleeds					
Roctavian (vs. SoC)	0.00	0.00	0.00	0.00	0.0000
Major bleeds					
Roctavian (vs. SoC)	0.00	0.00	0.00	0.00	0.0000
Life-threatening bleeds					
Roctavian (vs. SoC)	0.00	0.00	0.00	0.00	0.0000
Joint bleeds					
Roctavian (vs. SoC)	0.00	0.00	0.00	0.00	0.0000

Data source: DHR from Q1 2023 to Q3 2028

Acronyms: SoC: standard of care

Table 7 Proportion of Patients with Zero Bleeds, Roctavian and SoC Cohorts

Measures	Unadjusted						After SMRW					
	Roctavian Cohort N=		SoC Cohort N=		p-value (Roctavian vs. SoC)	Std. Diff. (Roctavian vs. SoC)	Roctavian Cohort N=		SoC Cohort N=		p-value (Roctavian vs. SoC)	Std. Diff. (Roctavian vs. SoC)
	N	(%)	N	(%)			N	(%)	N	(%)		
Patients with zero treated bleeds												
Overall	0	0.0%	0	0.0%	0.0000	0.00	0	0.0%	0	0.0%	0.0000	0.00
≥1 year follow-up	0	0.0%	0	0.0%	0.0000	0.00	0	0.0%	0	0.0%	0.0000	0.00
≥2 years follow-up	0	0.0%	0	0.0%	0.0000	0.00	0	0.0%	0	0.0%	0.0000	0.00
≥3 years follow-up	0	0.0%	0	0.0%	0.0000	0.00	0	0.0%	0	0.0%	0.0000	0.00
Patients with zero major bleeds												
Overall	0	0.0%	0	0.0%	0.0000	0.00	0	0.0%	0	0.0%	0.0000	0.00
≥1 year follow-up	0	0.0%	0	0.0%	0.0000	0.00	0	0.0%	0	0.0%	0.0000	0.00
≥2 years follow-up	0	0.0%	0	0.0%	0.0000	0.00	0	0.0%	0	0.0%	0.0000	0.00
≥3 years follow-up	0	0.0%	0	0.0%	0.0000	0.00	0	0.0%	0	0.0%	0.0000	0.00
Patients with zero life-threatening bleeds												
Overall	0	0.0%	0	0.0%	0.0000	0.00	0	0.0%	0	0.0%	0.0000	0.00
≥1 year follow-up	0	0.0%	0	0.0%	0.0000	0.00	0	0.0%	0	0.0%	0.0000	0.00
≥2 years follow-up	0	0.0%	0	0.0%	0.0000	0.00	0	0.0%	0	0.0%	0.0000	0.00
≥3 years follow-up	0	0.0%	0	0.0%	0.0000	0.00	0	0.0%	0	0.0%	0.0000	0.00
Patients with zero joint bleeds												
Overall	0	0.0%	0	0.0%	0.0000	0.00	0	0.0%	0	0.0%	0.0000	0.00
≥1 year follow-up	0	0.0%	0	0.0%	0.0000	0.00	0	0.0%	0	0.0%	0.0000	0.00
≥2 years follow-up	0	0.0%	0	0.0%	0.0000	0.00	0	0.0%	0	0.0%	0.0000	0.00
≥3 years follow-up	0	0.0%	0	0.0%	0.0000	0.00	0	0.0%	0	0.0%	0.0000	0.00

Data source: DHR from Q1 2023 to Q3 2028
Acronyms: SoC: standard of care
Note: Std. diff. examines the balance of covariate distribution between groups, with a value >0.1 indicating some imbalance between groups and >0.25 indicating poor balance.

Table 8 SMRW-Adjusted Logistic Regression Model of Patients with Zero Bleeds for the Overall Timeframe, Roctavian and SoC Cohorts

Unadjusted Logistic Regression Model

Measures	Odds Ratio	95% Confidence Limits		p-value
		Lower Limit	Upper Limit	
Zero treated bleeds				
Roctavian (vs. SoC)	0.00	0.00	0.00	0.0000
Zero major bleeds				
Roctavian (vs. SoC)	0.00	0.00	0.00	0.0000
Zero life-threatening bleeds				
Roctavian (vs. SoC)	0.00	0.00	0.00	0.0000
Zero joint bleeds				
Roctavian (vs. SoC)	0.00	0.00	0.00	0.0000

Adjusted Logistic Regression Model (if conducted)

Measures	Odds Ratio	95% Confidence Limits		p-value
		Lower Limit	Upper Limit	
Zero treated bleeds				
Roctavian (vs. SoC)	0.00	0.00	0.00	0.0000
Zero major bleeds				
Roctavian (vs. SoC)	0.00	0.00	0.00	0.0000
Zero life-threatening bleeds				
Roctavian (vs. SoC)	0.00	0.00	0.00	0.0000
Zero joint bleeds				
Roctavian (vs. SoC)	0.00	0.00	0.00	0.0000

Data source: DHR from Q1 2023 to Q3 2028

Acronyms: SoC: standard of care

Table 9 Hemostatic Medication Use for Roctavian and SoC Cohorts

Measures	Unadjusted										After SMRW									
	Roctavian Cohort		SoC Cohort		FVIII Sub-Cohort		Emicizumab Sub-Cohort		p-value (Roctavian vs. SoC)	Std. Diff. (Roctavian vs. SoC)	Roctavian Cohort		SoC Cohort		FVIII Sub-Cohort		Emicizumab Sub-Cohort		p-value (Roctavian vs. SoC)	Std. Diff. (Roctavian vs. SoC)
	N=		N=		N=		N=				N=		N=		N=		N=			
	N	(%)	N	(%)	N	(%)	N	(%)			N	(%)	N	(%)	N	(%)	N	(%)		
Patients with any hemostatic medication use																				
Overall	0	0.0%	0	0.0%	0	0.0%	0	0.0%			0	0.0%	0	0.0%	0	0.0%	0	0.0%		
≥1 year follow-up	0	0.0%	0	0.0%	0	0.0%	0	0.0%			0	0.0%	0	0.0%	0	0.0%	0	0.0%		
≥2 years follow-up	0	0.0%	0	0.0%	0	0.0%	0	0.0%			0	0.0%	0	0.0%	0	0.0%	0	0.0%		
≥3 years follow-up	0	0.0%	0	0.0%	0	0.0%	0	0.0%			0	0.0%	0	0.0%	0	0.0%	0	0.0%		
Patients with hemostatic medication use for bleeds or short-term prophylaxis																				
Overall	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0.0000	0.00	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0.0000	0.00
≥1 year follow-up	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0.0000	0.00	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0.0000	0.00
≥2 years follow-up	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0.0000	0.00	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0.0000	0.00
≥3 years follow-up	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0.0000	0.00	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0.0000	0.00
Infusion/ injection rate (number of infusions or injections/year)																				
Mean	0.00		0.00		0.00		0.00		0.0000	0.00	0.00		0.00		0.00		0.00		0.0000	0.00

Measures	Unadjusted										After SMRW									
	Roctavian Cohort		SoC Cohort		FVIII Sub-Cohort		Emicizumab Sub-Cohort		p-value (Roctavian vs. SoC)	Std. Diff. (Roctavian vs. SoC)	Roctavian Cohort		SoC Cohort		FVIII Sub-Cohort		Emicizumab Sub-Cohort		p-value (Roctavian vs. SoC)	Std. Diff. (Roctavian vs. SoC)
	N=		N=		N=		N=				N=		N=		N=		N=			
	N	(%)	N	(%)	N	(%)	N	(%)			N	(%)	N	(%)	N	(%)	N	(%)		
SD	0.00		0.00		0.00		0.00				0.00		0.00		0.00		0.00			
Median	0		0		0		0		0.0000		0		0		0		0		0.0000	
Q1	0		0		0		0				0		0		0		0			
Q3	0		0		0		0				0		0		0		0			
Min	0		0		0		0				0		0		0		0			
Max	0		0		0		0				0		0		0		0			
AIR																				
Mean	0.00		0.00		0.00		0.00		0.0000	0.00	0.00		0.00		0.00		0.00		0.0000	0.00
SD	0.00		0.00		0.00		0.00				0.00		0.00		0.00		0.00			
Median	0		0		0		0		0.0000		0		0		0		0		0.0000	
Q1	0		0		0		0				0		0		0		0			
Q3	0		0		0		0				0		0		0		0			
Min	0		0		0		0				0		0		0		0			
Max	0		0		0		0				0		0		0		0			
Prophylactic use																				
Total prophylactic FVIII utilization (IU)																				
Mean	0.00		0.00		0.00		0.00		0.0000	0.00	0.00		0.00		0.00		0.00		0.0000	0.00
SD	0.00		0.00		0.00		0.00				0.00		0.00		0.00		0.00			
Median	0		0		0		0		0.0000		0		0		0		0		0.0000	
Q1	0		0		0		0				0		0		0		0			
Q3	0		0		0		0				0		0		0		0			
Min	0		0		0		0				0		0		0		0			
Max	0		0		0		0				0		0		0		0			

Measures	Unadjusted										After SMRW									
	Roctavian Cohort		SoC Cohort		FVIII Sub-Cohort		Emicizumab Sub-Cohort		p-value (Roctavian vs. SoC)	Std. Diff. (Roctavian vs. SoC)	Roctavian Cohort		SoC Cohort		FVIII Sub-Cohort		Emicizumab Sub-Cohort		p-value (Roctavian vs. SoC)	Std. Diff. (Roctavian vs. SoC)
	N=		N=		N=		N=				N=		N=		N=		N=			
	N	(%)	N	(%)	N	(%)	N	(%)			N	(%)	N	(%)	N	(%)	N	(%)		
Total prophylactic FVIII utilization per patient per kg (IU/kg)																				
Mean	0.00		0.00		0.00		0.00		0.0000	0.00	0.00		0.00		0.00		0.00		0.0000	0.00
SD	0.00		0.00		0.00		0.00				0.00		0.00		0.00		0.00			
Median	0		0		0		0		0.0000		0		0		0		0		0.0000	
Q1	0		0		0		0				0		0		0		0			
Q3	0		0		0		0				0		0		0		0			
Min	0		0		0		0				0		0		0		0			
Max	0		0		0		0				0		0		0		0			
Total prophylactic emicizumab utilization (mg)																				
Mean	0.00		0.00		0.00		0.00		0.0000	0.00	0.00		0.00		0.00		0.00		0.0000	0.00
SD	0.00		0.00		0.00		0.00				0.00		0.00		0.00		0.00			
Median	0		0		0		0		0.0000		0		0		0		0		0.0000	
Q1	0		0		0		0				0		0		0		0			
Q3	0		0		0		0				0		0		0		0			
Min	0		0		0		0				0		0		0		0			
Max	0		0		0		0				0		0		0		0			
Total prophylactic emicizumab utilization per patient per kg (mg/kg)																				
Mean	0.00		0.00		0.00		0.00		0.0000	0.00	0.00		0.00		0.00		0.00		0.0000	0.00
SD	0.00		0.00		0.00		0.00				0.00		0.00		0.00		0.00			

Measures	Unadjusted										After SMRW									
	Roctavian Cohort		SoC Cohort		FVIII Sub-Cohort		Emicizumab Sub-Cohort		p-value (Roctavian vs. SoC)	Std. Diff. (Roctavian vs. SoC)	Roctavian Cohort		SoC Cohort		FVIII Sub-Cohort		Emicizumab Sub-Cohort		p-value (Roctavian vs. SoC)	Std. Diff. (Roctavian vs. SoC)
	N=		N=		N=		N=				N=		N=		N=		N=			
	N	(%)	N	(%)	N	(%)	N	(%)			N	(%)	N	(%)	N	(%)	N	(%)		
Median	0		0		0		0		0.0000		0		0		0		0		0.0000	
Q1	0		0		0		0				0		0		0		0			
Q3	0		0		0		0				0		0		0		0			
Min	0		0		0		0				0		0		0		0			
Max	0		0		0		0				0		0		0		0			
On-demand use for bleeds																				
Total on-demand FVIII utilization for bleed (IU)																				
Mean	0.00		0.00		0.00		0.00		0.0000	0.00	0.00		0.00		0.00		0.00		0.0000	0.00
SD	0.00		0.00		0.00		0.00				0.00		0.00		0.00		0.00			
Median	0		0		0		0		0.0000		0		0		0		0		0.0000	
Q1	0		0		0		0				0		0		0		0			
Q3	0		0		0		0				0		0		0		0			
Min	0		0		0		0				0		0		0		0			
Max	0		0		0		0				0		0		0		0			
Total on-demand FVIII utilization per patient per kg for bleed (IU/kg)																				
Mean	0.00		0.00		0.00		0.00		0.0000	0.00	0.00		0.00		0.00		0.00		0.0000	0.00
SD	0.00		0.00		0.00		0.00				0.00		0.00		0.00		0.00			
Median	0		0		0		0		0.0000		0		0		0		0		0.0000	
Q1	0		0		0		0				0		0		0		0			
Q3	0		0		0		0				0		0		0		0			
Min	0		0		0		0				0		0		0		0			
Max	0		0		0		0				0		0		0		0			

Measures	Unadjusted										After SMRW									
	Roctavian Cohort		SoC Cohort		FVIII Sub-Cohort		Emicizumab Sub-Cohort		p-value (Roctavian vs. SoC)	Std. Diff. (Roctavian vs. SoC)	Roctavian Cohort		SoC Cohort		FVIII Sub-Cohort		Emicizumab Sub-Cohort		p-value (Roctavian vs. SoC)	Std. Diff. (Roctavian vs. SoC)
	N=		N=		N=		N=				N=		N=		N=		N=			
	N	(%)	N	(%)	N	(%)	N	(%)			N	(%)	N	(%)	N	(%)	N	(%)		
Total on-demand emicizumab utilization for bleed (mg)																				
Mean	0.00		0.00		0.00		0.00		0.0000	0.00	0.00		0.00		0.00		0.00		0.0000	0.00
SD	0.00		0.00		0.00		0.00				0.00		0.00		0.00		0.00			
Median	0		0		0		0		0.0000		0		0		0		0		0.0000	
Q1	0		0		0		0				0		0		0		0			
Q3	0		0		0		0				0		0		0		0			
Min	0		0		0		0				0		0		0		0			
Max	0		0		0		0				0		0		0		0			
Total on-demand emicizumab utilization per patient per kg for bleed (mg/kg)																				
Mean	0.00		0.00		0.00		0.00		0.0000	0.00	0.00		0.00		0.00		0.00		0.0000	0.00
SD	0.00		0.00		0.00		0.00				0.00		0.00		0.00		0.00			
Median	0		0		0		0		0.0000		0		0		0		0		0.0000	
Q1	0		0		0		0				0		0		0		0			
Q3	0		0		0		0				0		0		0		0			
Min	0		0		0		0				0		0		0		0			
Max	0		0		0		0				0		0		0		0			
Total on-demand FVIII utilization for short-term prophylaxis (IU)																				
Mean	0.00		0.00		0.00		0.00		0.0000	0.00	0.00		0.00		0.00		0.00		0.0000	0.00

Measures	Unadjusted										After SMRW									
	Roctavian Cohort		SoC Cohort		FVIII Sub-Cohort		Emicizumab Sub-Cohort		p-value (Roctavian vs. SoC)	Std. Diff. (Roctavian vs. SoC)	Roctavian Cohort		SoC Cohort		FVIII Sub-Cohort		Emicizumab Sub-Cohort		p-value (Roctavian vs. SoC)	Std. Diff. (Roctavian vs. SoC)
	N=		N=		N=		N=				N=		N=		N=		N=			
	N	(%)	N	(%)	N	(%)	N	(%)			N	(%)	N	(%)	N	(%)	N	(%)		
SD	0.00		0.00		0.00		0.00				0.00		0.00		0.00		0.00			
Median	0		0		0		0		0.0000		0		0		0		0		0.0000	
Q1	0		0		0		0				0		0		0		0			
Q3	0		0		0		0				0		0		0		0			
Min	0		0		0		0				0		0		0		0			
Max	0		0		0		0				0		0		0		0			
On-demand use for short-term prophylaxis																				
Total on-demand FVIII utilization per patient per kg for short-term prophylaxis (IU/kg)																				
Mean	0.00		0.00		0.00		0.00		0.0000	0.00	0.00		0.00		0.00		0.00		0.0000	0.00
SD	0.00		0.00		0.00		0.00				0.00		0.00		0.00		0.00			
Median	0		0		0		0		0.0000		0		0		0		0		0.0000	
Q1	0		0		0		0				0		0		0		0			
Q3	0		0		0		0				0		0		0		0			
Min	0		0		0		0				0		0		0		0			
Max	0		0		0		0				0		0		0		0			
Total on-demand emicizumab utilization for short-term prophylaxis (mg)																				
Mean	0.00		0.00		0.00		0.00		0.0000	0.00	0.00		0.00		0.00		0.00		0.0000	0.00
SD	0.00		0.00		0.00		0.00				0.00		0.00		0.00		0.00			
Median	0		0		0		0		0.0000		0		0		0		0		0.0000	

Measures	Unadjusted										After SMRW									
	Roctavian Cohort		SoC Cohort		FVIII Sub-Cohort		Emicizumab Sub-Cohort		p-value (Roctavian vs. SoC)	Std. Diff. (Roctavian vs. SoC)	Roctavian Cohort		SoC Cohort		FVIII Sub-Cohort		Emicizumab Sub-Cohort		p-value (Roctavian vs. SoC)	Std. Diff. (Roctavian vs. SoC)
	N=		N=		N=		N=				N=		N=		N=		N=			
	N	(%)	N	(%)	N	(%)	N	(%)			N	(%)	N	(%)	N	(%)	N	(%)		
Q1	0		0		0		0				0		0		0		0			
Q3	0		0		0		0				0		0		0		0			
Min	0		0		0		0				0		0		0		0			
Max	0		0		0		0				0		0		0		0			
Total on-demand emicizumab utilization per patient per kg for short-term prophylaxis (mg/kg)																				
Mean	0.00		0.00		0.00		0.00		0.0000	0.00	0.00		0.00		0.00		0.00		0.0000	0.00
SD	0.00		0.00		0.00		0.00				0.00		0.00		0.00		0.00			
Median	0		0		0		0		0.0000		0		0		0		0		0.0000	
Q1	0		0		0		0				0		0		0		0			
Q3	0		0		0		0				0		0		0		0			
Min	0		0		0		0				0		0		0		0			
Max	0		0		0		0				0		0		0		0			

Data source: DHR from Q1 2023 to Q3 2028
Acronyms: SoC: standard of care; AIR: annualized infusion/injection rate; FVIII: coagulation factor VIII; IU: international units; kg: kilogram; mg: milligram
Note: Std. diff. examines the balance of covariate distribution between groups, with a value >0.1 indicating some imbalance between groups and >0.25 indicating poor balance.

Table 10 COAs for Roctavian and SoC Cohorts – HJHS

Measures	Unadjusted						After SMRW					
	Roctavian Cohort		SoC Cohort		p-value (Roctavian vs. SoC)	Std. Diff. (Roctavian vs. SoC)	Roctavian Cohort		SoC Cohort		p-value (Roctavian vs. SoC)	Std. Diff. (Roctavian vs. SoC)
	N=		N=				N=		N=			
	N	(%)	N	(%)			N	(%)	N	(%)		
Baseline												

Measures	Unadjusted						After SMRW					
	Roctavian Cohort N=		SoC Cohort N=		p-value (Roctavian vs. SoC)	Std. Diff. (Roctavian vs. SoC)	Roctavian Cohort N=		SoC Cohort N=		p-value (Roctavian vs. SoC)	Std. Diff. (Roctavian vs. SoC)
	N	(%)	N	(%)			N	(%)	N	(%)		
Left elbow	0	0.0%	0	0.0%	0.0000	0.00	0	0.0%	0	0.0%	0.0000	0.00
Mean	0.00		0.00		0.0000	0.00	0.00		0.00		0.0000	0.00
SD	0.00		0.00				0.00		0.00			
Median	0		0		0.0000		0		0		0.0000	
Q1	0		0				0		0			
Q3	0		0				0		0			
Min	0		0				0		0			
Max	0		0				0		0			
Right elbow	0	0.0%	0	0.0%	0.0000	0.00	0	0.0%	0	0.0%	0.0000	0.00
Mean	0.00		0.00		0.0000	0.00	0.00		0.00		0.0000	0.00
SD	0.00		0.00				0.00		0.00			
Median	0		0		0.0000		0		0		0.0000	
Q1	0		0				0		0			
Q3	0		0				0		0			
Min	0		0				0		0			
Max	0		0				0		0			
Left knee	0	0.0%	0	0.0%	0.0000	0.00	0	0.0%	0	0.0%	0.0000	0.00
Mean	0.00		0.00		0.0000	0.00	0.00		0.00		0.0000	0.00
SD	0.00		0.00				0.00		0.00			
Median	0		0		0.0000		0		0		0.0000	
Q1	0		0				0		0			
Q3	0		0				0		0			
Min	0		0				0		0			
Max	0		0				0		0			
Right knee	0	0.0%	0	0.0%	0.0000	0.00	0	0.0%	0	0.0%	0.0000	0.00
Mean	0.00		0.00		0.0000	0.00	0.00		0.00		0.0000	0.00
SD	0.00		0.00				0.00		0.00			
Median	0		0		0.0000		0		0		0.0000	
Q1	0		0				0		0			
Q3	0		0				0		0			
Min	0		0				0		0			
Max	0		0				0		0			

Measures	Unadjusted						After SMRW					
	Roctavian Cohort N=		SoC Cohort N=		p-value (Roctavian vs. SoC)	Std. Diff. (Roctavian vs. SoC)	Roctavian Cohort N=		SoC Cohort N=		p-value (Roctavian vs. SoC)	Std. Diff. (Roctavian vs. SoC)
	N	(%)	N	(%)			N	(%)	N	(%)		
Left ankle	0	0.0%	0	0.0%	0.0000	0.00	0	0.0%	0	0.0%	0.0000	0.00
Mean	0.00		0.00		0.0000	0.00	0.00		0.00		0.0000	0.00
SD	0.00		0.00				0.00		0.00			
Median	0		0		0.0000		0		0		0.0000	
Q1	0		0				0		0			
Q3	0		0				0		0			
Min	0		0				0		0			
Max	0		0				0		0			
Right ankle	0	0.0%	0	0.0%	0.0000	0.00	0	0.0%	0	0.0%	0.0000	0.00
Mean	0.00		0.00		0.0000	0.00	0.00		0.00		0.0000	0.00
SD	0.00		0.00				0.00		0.00			
Median	0		0		0.0000		0		0		0.0000	
Q1	0		0				0		0			
Q3	0		0				0		0			
Min	0		0				0		0			
Max	0		0				0		0			
Global gait score	0	0.0%	0	0.0%	0.0000	0.00	0	0.0%	0	0.0%	0.0000	0.00
Mean	0.00		0.00		0.0000	0.00	0.00		0.00		0.0000	0.00
SD	0.00		0.00				0.00		0.00			
Median	0		0		0.0000		0		0		0.0000	
Q1	0		0				0		0			
Q3	0		0				0		0			
Min	0		0				0		0			
Max	0		0				0		0			
Total score	0	0.0%	0	0.0%	0.0000	0.00	0	0.0%	0	0.0%	0.0000	0.00
Mean	0.00		0.00		0.0000	0.00	0.00		0.00		0.0000	0.00
SD	0.00		0.00				0.00		0.00			
Median	0		0		0.0000		0		0		0.0000	
Q1	0		0				0		0			
Q3	0		0				0		0			
Min	0		0				0		0			
Max	0		0				0		0			

Measures	Unadjusted						After SMRW					
	Roctavian Cohort N=		SoC Cohort N=		p-value (Roctavian vs. SoC)	Std. Diff. (Roctavian vs. SoC)	Roctavian Cohort N=		SoC Cohort N=		p-value (Roctavian vs. SoC)	Std. Diff. (Roctavian vs. SoC)
	N	(%)	N	(%)			N	(%)	N	(%)		
Follow-Up												
Length of follow-up	0	0.0%	0	0.0%	0.0000	0.00	0	0.0%	0	0.0%	0.0000	0.00
Mean	0.00		0.00		0.0000	0.00	0.00		0.00		0.0000	0.00
SD	0.00		0.00				0.00		0.00			
Median	0		0		0.0000		0		0		0.0000	
Q1	0		0				0		0			
Q3	0		0				0		0			
Min	0		0				0		0			
Max	0		0				0		0			
Left elbow	0	0.0%	0	0.0%	0.0000	0.00	0	0.0%	0	0.0%	0.0000	0.00
Mean	0.00		0.00		0.0000	0.00	0.00		0.00		0.0000	0.00
SD	0.00		0.00				0.00		0.00			
Median	0		0		0.0000		0		0		0.0000	
Q1	0		0				0		0			
Q3	0		0				0		0			
Min	0		0				0		0			
Max	0		0				0		0			
Right elbow	0	0.0%	0	0.0%	0.0000	0.00	0	0.0%	0	0.0%	0.0000	0.00
Mean	0.00		0.00		0.0000	0.00	0.00		0.00		0.0000	0.00
SD	0.00		0.00				0.00		0.00			
Median	0		0		0.0000		0		0		0.0000	
Q1	0		0				0		0			
Q3	0		0				0		0			
Min	0		0				0		0			
Max	0		0				0		0			
Left knee	0	0.0%	0	0.0%	0.0000	0.00	0	0.0%	0	0.0%	0.0000	0.00
Mean	0.00		0.00		0.0000	0.00	0.00		0.00		0.0000	0.00
SD	0.00		0.00				0.00		0.00			
Median	0		0		0.0000		0		0		0.0000	
Q1	0		0				0		0			
Q3	0		0				0		0			

Measures	Unadjusted						After SMRW					
	Roctavian Cohort N=		SoC Cohort N=		p-value (Roctavian vs. SoC)	Std. Diff. (Roctavian vs. SoC)	Roctavian Cohort N=		SoC Cohort N=		p-value (Roctavian vs. SoC)	Std. Diff. (Roctavian vs. SoC)
	N	(%)	N	(%)			N	(%)	N	(%)		
Min	0		0				0		0			
Max	0		0				0		0			
Right knee	0	0.0%	0	0.0%	0.0000	0.00	0	0.0%	0	0.0%	0.0000	0.00
Mean	0.00		0.00		0.0000	0.00	0.00		0.00		0.0000	0.00
SD	0.00		0.00				0.00		0.00			
Median	0		0		0.0000		0		0		0.0000	
Q1	0		0				0		0			
Q3	0		0				0		0			
Min	0		0				0		0			
Max	0		0				0		0			
Left ankle	0	0.0%	0	0.0%	0.0000	0.00	0	0.0%	0	0.0%	0.0000	0.00
Mean	0.00		0.00		0.0000	0.00	0.00		0.00		0.0000	0.00
SD	0.00		0.00				0.00		0.00			
Median	0		0		0.0000		0		0		0.0000	
Q1	0		0				0		0			
Q3	0		0				0		0			
Min	0		0				0		0			
Max	0		0				0		0			
Right ankle	0	0.0%	0	0.0%	0.0000	0.00	0	0.0%	0	0.0%	0.0000	0.00
Mean	0.00		0.00		0.0000	0.00	0.00		0.00		0.0000	0.00
SD	0.00		0.00				0.00		0.00			
Median	0		0		0.0000		0		0		0.0000	
Q1	0		0				0		0			
Q3	0		0				0		0			
Min	0		0				0		0			
Max	0		0				0		0			
Global gait score	0	0.0%	0	0.0%	0.0000	0.00	0	0.0%	0	0.0%	0.0000	0.00
Mean	0.00		0.00		0.0000	0.00	0.00		0.00		0.0000	0.00
SD	0.00		0.00				0.00		0.00			
Median	0		0		0.0000		0		0		0.0000	
Q1	0		0				0		0			

Measures	Unadjusted						After SMRW					
	Roctavian Cohort N=		SoC Cohort N=		p-value (Roctavian vs. SoC)	Std. Diff. (Roctavian vs. SoC)	Roctavian Cohort N=		SoC Cohort N=		p-value (Roctavian vs. SoC)	Std. Diff. (Roctavian vs. SoC)
	N	(%)	N	(%)			N	(%)	N	(%)		
Q3	0		0				0		0			
Min	0		0				0		0			
Max	0		0				0		0			
Total score	0	0.0%	0	0.0%	0.0000	0.00	0	0.0%	0	0.0%	0.0000	0.00
Mean	0.00		0.00		0.0000	0.00	0.00		0.00		0.0000	0.00
SD	0.00		0.00				0.00		0.00			
Median	0		0		0.0000		0		0		0.0000	
Q1	0		0				0		0			
Q3	0		0				0		0			
Min	0		0				0		0			
Max	0		0				0		0			
Change From Baseline												
Left elbow	0	0.0%	0	0.0%	0.0000	0.00	0	0.0%	0	0.0%	0.0000	0.00
Mean	0.00		0.00		0.0000	0.00	0.00		0.00		0.0000	0.00
SD	0.00		0.00				0.00		0.00			
Median	0		0		0.0000		0		0		0.0000	
Q1	0		0				0		0			
Q3	0		0				0		0			
Min	0		0				0		0			
Max	0		0				0		0			
Right elbow	0	0.0%	0	0.0%	0.0000	0.00	0	0.0%	0	0.0%	0.0000	0.00
Mean	0.00		0.00		0.0000	0.00	0.00		0.00		0.0000	0.00
SD	0.00		0.00				0.00		0.00			
Median	0		0		0.0000		0		0		0.0000	
Q1	0		0				0		0			
Q3	0		0				0		0			
Min	0		0				0		0			
Max	0		0				0		0			
Left knee	0	0.0%	0	0.0%	0.0000	0.00	0	0.0%	0	0.0%	0.0000	0.00
Mean	0.00		0.00		0.0000	0.00	0.00		0.00		0.0000	0.00
SD	0.00		0.00				0.00		0.00			
Median	0		0		0.0000		0		0		0.0000	

Measures	Unadjusted						After SMRW					
	Roctavian Cohort N=		SoC Cohort N=		p-value (Roctavian vs. SoC)	Std. Diff. (Roctavian vs. SoC)	Roctavian Cohort N=		SoC Cohort N=		p-value (Roctavian vs. SoC)	Std. Diff. (Roctavian vs. SoC)
	N	(%)	N	(%)			N	(%)	N	(%)		
Q1	0		0				0		0			
Q3	0		0				0		0			
Min	0		0				0		0			
Max	0		0				0		0			
Right knee	0	0.0%	0	0.0%	0.0000	0.00	0	0.0%	0	0.0%	0.0000	0.00
Mean	0.00		0.00		0.0000	0.00	0.00		0.00		0.0000	0.00
SD	0.00		0.00				0.00		0.00			
Median	0		0		0.0000		0		0		0.0000	
Q1	0		0				0		0			
Q3	0		0				0		0			
Min	0		0				0		0			
Max	0		0				0		0			
Left ankle	0	0.0%	0	0.0%	0.0000	0.00	0	0.0%	0	0.0%	0.0000	0.00
Mean	0.00		0.00		0.0000	0.00	0.00		0.00		0.0000	0.00
SD	0.00		0.00				0.00		0.00			
Median	0		0		0.0000		0		0		0.0000	
Q1	0		0				0		0			
Q3	0		0				0		0			
Min	0		0				0		0			
Max	0		0				0		0			
Right ankle	0	0.0%	0	0.0%	0.0000	0.00	0	0.0%	0	0.0%	0.0000	0.00
Mean	0.00		0.00		0.0000	0.00	0.00		0.00		0.0000	0.00
SD	0.00		0.00				0.00		0.00			
Median	0		0		0.0000		0		0		0.0000	
Q1	0		0				0		0			
Q3	0		0				0		0			
Min	0		0				0		0			
Max	0		0				0		0			
Global gait score	0	0.0%	0	0.0%	0.0000	0.00	0	0.0%	0	0.0%	0.0000	0.00
Mean	0.00		0.00		0.0000	0.00	0.00		0.00		0.0000	0.00
SD	0.00		0.00				0.00		0.00			

Measures	Unadjusted						After SMRW					
	Roctavian Cohort N=		SoC Cohort N=		p-value (Roctavian vs. SoC)	Std. Diff. (Roctavian vs. SoC)	Roctavian Cohort N=		SoC Cohort N=		p-value (Roctavian vs. SoC)	Std. Diff. (Roctavian vs. SoC)
	N	(%)	N	(%)			N	(%)	N	(%)		
Median	0		0		0.0000		0		0		0.0000	
Q1	0		0				0		0			
Q3	0		0				0		0			
Min	0		0				0		0			
Max	0		0				0		0			
Total score	0	0.0%	0	0.0%	0.0000	0.00	0	0.0%	0	0.0%	0.0000	0.00
Mean	0.00		0.00		0.0000	0.00	0.00		0.00		0.0000	0.00
SD	0.00		0.00				0.00		0.00			
Median	0		0		0.0000		0		0		0.0000	
Q1	0		0				0		0			
Q3	0		0				0		0			
Min	0		0				0		0			
Max	0		0				0		0			

Data source: DHR from Q1 2023 to Q3 2028

Acronyms: SoC: standard of care; COA: clinical outcome assessment; SD: standard deviation; HJHS: Hemophilia Joint Health Score

Note: Std. diff. examines the balance of covariate distribution between groups, with a value >0.1 indicating some imbalance between groups and >0.25 indicating poor balance.

Table 11 COAs for Roctavian and SoC Cohorts – Haemo-QoL-A

	Unadjusted						After SMRW					
	Roctavian Cohort N=		SoC Cohort N=		p-value (Roctavian vs. SoC)	Std. Diff. (Roctavian vs. SoC)	Roctavian Cohort N=		SoC Cohort N=		p-value (Roctavian vs. SoC)	Std. Diff. (Roctavian vs. SoC)
	N	(%)	N	(%)			N	(%)	N	(%)		
Baseline												
Physical functioning	0	0.0%	0	0.0%	0.0000	0.00	0	0.0%	0	0.0%	0.0000	0.00
Mean	0.00		0.00		0.0000	0.00	0.00		0.00		0.0000	0.00
SD	0.00		0.00				0.00		0.00			
Median	0		0		0.0000		0		0		0.0000	
Q1	0		0				0		0			
Q3	0		0				0		0			
Min	0		0				0		0			
Max	0		0				0		0			
Role functioning	0	0.0%	0	0.0%	0.0000	0.00	0	0.0%	0	0.0%	0.0000	0.00
Mean	0.00		0.00		0.0000	0.00	0.00		0.00		0.0000	0.00
SD	0.00		0.00				0.00		0.00			
Median	0		0		0.0000		0		0		0.0000	
Q1	0		0				0		0			
Q3	0		0				0		0			
Min	0		0				0		0			
Max	0		0				0		0			
Worry	0	0.0%	0	0.0%	0.0000	0.00	0	0.0%	0	0.0%	0.0000	0.00
Mean	0.00		0.00		0.0000	0.00	0.00		0.00		0.0000	0.00
SD	0.00		0.00				0.00		0.00			
Median	0		0		0.0000		0		0		0.0000	
Q1	0		0				0		0			
Q3	0		0				0		0			
Min	0		0				0		0			
Max	0		0				0		0			
Consequences of bleeding	0	0.0%	0	0.0%	0.0000	0.00	0	0.0%	0	0.0%	0.0000	0.00
Mean	0.00		0.00		0.0000	0.00	0.00		0.00		0.0000	0.00
SD	0.00		0.00				0.00		0.00			
Median	0		0		0.0000		0		0		0.0000	

	Unadjusted						After SMRW					
	Roctavian Cohort N=		SoC Cohort N=		p-value (Roctavian vs. SoC)	Std. Diff. (Roctavian vs. SoC)	Roctavian Cohort N=		SoC Cohort N=		p-value (Roctavian vs. SoC)	Std. Diff. (Roctavian vs. SoC)
	N	(%)	N	(%)			N	(%)	N	(%)		
Q1	0		0				0		0			
Q3	0		0				0		0			
Min	0		0				0		0			
Max	0		0				0		0			
Emotional impact	0	0.0%	0	0.0%	0.0000	0.00	0	0.0%	0	0.0%	0.0000	0.00
Mean	0.00		0.00		0.0000	0.00	0.00		0.00		0.0000	0.00
SD	0.00		0.00				0.00		0.00			
Median	0		0		0.0000		0		0		0.0000	
Q1	0		0				0		0			
Q3	0		0				0		0			
Min	0		0				0		0			
Max	0		0				0		0			
Treatment concerns	0	0.0%	0	0.0%	0.0000	0.00	0	0.0%	0	0.0%	0.0000	0.00
Mean	0.00		0.00		0.0000	0.00	0.00		0.00		0.0000	0.00
SD	0.00		0.00				0.00		0.00			
Median	0		0		0.0000		0		0		0.0000	
Q1	0		0				0		0			
Q3	0		0				0		0			
Min	0		0				0		0			
Max	0		0				0		0			
Total score	0	0.0%	0	0.0%	0.0000	0.00	0	0.0%	0	0.0%	0.0000	0.00
Mean	0.00		0.00		0.0000	0.00	0.00		0.00		0.0000	0.00
SD	0.00		0.00				0.00		0.00			
Median	0		0		0.0000		0		0		0.0000	
Q1	0		0				0		0			
Q3	0		0				0		0			
Min	0		0				0		0			
Max	0		0				0		0			
Follow-Up												
Length of follow-up	0	0.0%	0	0.0%	0.0000	0.00	0	0.0%	0	0.0%	0.0000	0.00
Mean	0.00		0.00		0.0000	0.00	0.00		0.00		0.0000	0.00

	Unadjusted						After SMRW					
	Roctavian Cohort N=		SoC Cohort N=		p-value (Roctavian vs. SoC)	Std. Diff. (Roctavian vs. SoC)	Roctavian Cohort N=		SoC Cohort N=		p-value (Roctavian vs. SoC)	Std. Diff. (Roctavian vs. SoC)
	N	(%)	N	(%)			N	(%)	N	(%)		
SD	0.00		0.00				0.00		0.00			
Median	0		0		0.0000		0		0		0.0000	
Q1	0		0				0		0			
Q3	0		0				0		0			
Min	0		0				0		0			
Max	0		0				0		0			
Physical functioning	0	0.0%	0	0.0%	0.0000	0.00	0	0.0%	0	0.0%	0.0000	0.00
Mean	0.00		0.00		0.0000	0.00	0.00		0.00		0.0000	0.00
SD	0.00		0.00				0.00		0.00			
Median	0		0		0.0000		0		0		0.0000	
Q1	0		0				0		0			
Q3	0		0				0		0			
Min	0		0				0		0			
Max	0		0				0		0			
Role functioning	0	0.0%	0	0.0%	0.0000	0.00	0	0.0%	0	0.0%	0.0000	0.00
Mean	0.00		0.00		0.0000	0.00	0.00		0.00		0.0000	0.00
SD	0.00		0.00				0.00		0.00			
Median	0		0		0.0000		0		0		0.0000	
Q1	0		0				0		0			
Q3	0		0				0		0			
Min	0		0				0		0			
Max	0		0				0		0			
Worry	0	0.0%	0	0.0%	0.0000	0.00	0	0.0%	0	0.0%	0.0000	0.00
Mean	0.00		0.00		0.0000	0.00	0.00		0.00		0.0000	0.00
SD	0.00		0.00				0.00		0.00			
Median	0		0		0.0000		0		0		0.0000	
Q1	0		0				0		0			
Q3	0		0				0		0			
Min	0		0				0		0			
Max	0		0				0		0			

	Unadjusted						After SMRW					
	Roctavian Cohort		SoC Cohort		p-value (Roctavian vs. SoC)	Std. Diff. (Roctavian vs. SoC)	Roctavian Cohort		SoC Cohort		p-value (Roctavian vs. SoC)	Std. Diff. (Roctavian vs. SoC)
	N=		N=				N=		N=			
	N	(%)	N	(%)			N	(%)	N	(%)		
Consequences of bleeding	0	0.0%	0	0.0%	0.0000	0.00	0	0.0%	0	0.0%	0.0000	0.00
Mean	0.00		0.00		0.0000	0.00	0.00		0.00		0.0000	0.00
SD	0.00		0.00				0.00		0.00			
Median	0		0		0.0000		0		0		0.0000	
Q1	0		0				0		0			
Q3	0		0				0		0			
Min	0		0				0		0			
Max	0		0				0		0			
Emotional impact	0	0.0%	0	0.0%	0.0000	0.00	0	0.0%	0	0.0%	0.0000	0.00
Mean	0.00		0.00		0.0000	0.00	0.00		0.00		0.0000	0.00
SD	0.00		0.00				0.00		0.00			
Median	0		0		0.0000		0		0		0.0000	
Q1	0		0				0		0			
Q3	0		0				0		0			
Min	0		0				0		0			
Max	0		0				0		0			
Treatment concerns	0	0.0%	0	0.0%	0.0000	0.00	0	0.0%	0	0.0%	0.0000	0.00
Mean	0.00		0.00		0.0000	0.00	0.00		0.00		0.0000	0.00
SD	0.00		0.00				0.00		0.00			
Median	0		0		0.0000		0		0		0.0000	
Q1	0		0				0		0			
Q3	0		0				0		0			
Min	0		0				0		0			
Max	0		0				0		0			
Total score	0	0.0%	0	0.0%	0.0000	0.00	0	0.0%	0	0.0%	0.0000	0.00
Mean	0.00		0.00		0.0000	0.00	0.00		0.00		0.0000	0.00
SD	0.00		0.00				0.00		0.00			
Median	0		0		0.0000		0		0		0.0000	
Q1	0		0				0		0			
Q3	0		0				0		0			
Min	0		0				0		0			

	Unadjusted						After SMRW					
	Roctavian Cohort		SoC Cohort		p-value (Roctavian vs. SoC)	Std. Diff. (Roctavian vs. SoC)	Roctavian Cohort		SoC Cohort		p-value (Roctavian vs. SoC)	Std. Diff. (Roctavian vs. SoC)
	N=		N=				N=		N=			
	N	(%)	N	(%)			N	(%)	N	(%)		
Max	0		0				0		0			
Change from Follow-Up												
Physical functioning	0	0.0%	0	0.0%	0.0000	0.00	0	0.0%	0	0.0%	0.0000	0.00
Mean	0.00		0.00		0.0000	0.00	0.00		0.00		0.0000	0.00
SD	0.00		0.00				0.00		0.00			
Median	0		0		0.0000		0		0		0.0000	
Q1	0		0				0		0			
Q3	0		0				0		0			
Min	0		0				0		0			
Max	0		0				0		0			
Role functioning	0	0.0%	0	0.0%	0.0000	0.00	0	0.0%	0	0.0%	0.0000	0.00
Mean	0.00		0.00		0.0000	0.00	0.00		0.00		0.0000	0.00
SD	0.00		0.00				0.00		0.00			
Median	0		0		0.0000		0		0		0.0000	
Q1	0		0				0		0			
Q3	0		0				0		0			
Min	0		0				0		0			
Max	0		0				0		0			
Worry	0	0.0%	0	0.0%	0.0000	0.00	0	0.0%	0	0.0%	0.0000	0.00
Mean	0.00		0.00		0.0000	0.00	0.00		0.00		0.0000	0.00
SD	0.00		0.00				0.00		0.00			
Median	0		0		0.0000		0		0		0.0000	
Q1	0		0				0		0			
Q3	0		0				0		0			
Min	0		0				0		0			
Max	0		0				0		0			
Consequences of bleeding	0	0.0%	0	0.0%	0.0000	0.00	0	0.0%	0	0.0%	0.0000	0.00
Mean	0.00		0.00		0.0000	0.00	0.00		0.00		0.0000	0.00
SD	0.00		0.00				0.00		0.00			
Median	0		0		0.0000		0		0		0.0000	

	Unadjusted						After SMRW					
	Roctavian Cohort		SoC Cohort		p-value (Roctavian vs. SoC)	Std. Diff. (Roctavian vs. SoC)	Roctavian Cohort		SoC Cohort		p-value (Roctavian vs. SoC)	Std. Diff. (Roctavian vs. SoC)
	N=		N=				N=		N=			
	N	(%)	N	(%)			N	(%)	N	(%)		
Q1	0		0				0		0			
Q3	0		0				0		0			
Min	0		0				0		0			
Max	0		0				0		0			
Emotional impact	0	0.0%	0	0.0%	0.0000	0.00	0	0.0%	0	0.0%	0.0000	0.00
Mean	0.00		0.00		0.0000	0.00	0.00		0.00		0.0000	0.00
SD	0.00		0.00				0.00		0.00			
Median	0		0		0.0000		0		0		0.0000	
Q1	0		0				0		0			
Q3	0		0				0		0			
Min	0		0				0		0			
Max	0		0				0		0			
Treatment concerns	0	0.0%	0	0.0%	0.0000	0.00	0	0.0%	0	0.0%	0.0000	0.00
Mean	0.00		0.00		0.0000	0.00	0.00		0.00		0.0000	0.00
SD	0.00		0.00				0.00		0.00			
Median	0		0		0.0000		0		0		0.0000	
Q1	0		0				0		0			
Q3	0		0				0		0			
Min	0		0				0		0			
Max	0		0				0		0			
Total score	0	0.0%	0	0.0%	0.0000	0.00	0	0.0%	0	0.0%	0.0000	0.00
Mean	0.00		0.00		0.0000	0.00	0.00		0.00		0.0000	0.00
SD	0.00		0.00				0.00		0.00			
Median	0		0		0.0000		0		0		0.0000	
Q1	0		0				0		0			
Q3	0		0				0		0			
Min	0		0				0		0			
Max	0		0				0		0			

Data source: DHR from Q1 2023 to Q3 2028
Acronyms: SoC: standard of care; COA: clinical outcome assessment; SD: standard deviation

	Unadjusted						After SMRW					
	Roctavian Cohort		SoC Cohort		p-value (Roctavian vs. SoC)	Std. Diff. (Roctavian vs. SoC)	Roctavian Cohort		SoC Cohort		p-value (Roctavian vs. SoC)	Std. Diff. (Roctavian vs. SoC)
	N=		N=				N=		N=			
	N	(%)	N	(%)			N	(%)	N	(%)		

Note: Std. diff. examines the balance of covariate distribution between groups, with a value >0.1 indicating some imbalance between groups and >0.25 indicating poor balance.

Table 12 COAs for Roctavian and SoC Cohorts – BPI-sf

Measures	Unadjusted						After SMRW					
	Roctavian Cohort N=		SoC Cohort N=		p-value (Roctavian vs. SoC)	Std. Diff. (Roctavian vs. SoC)	Roctavian Cohort N=		SoC Cohort N=		p-value (Roctavian vs. SoC)	Std. Diff. (Roctavian vs. SoC)
	N	(%)	N	(%)			N	(%)	N	(%)		
Baseline												
Pain intensity (Question 3)	0	0.0%	0	0.0%	0.0000	0.00	0	0.0%	0	0.0%	0.0000	0.00
Mean	0.00		0.00		0.0000	0.00	0.00		0.00		0.0000	0.00
SD	0.00		0.00				0.00		0.00			
Median	0		0		0.0000		0		0		0.0000	
Q1	0		0				0		0			
Q3	0		0				0		0			
Min	0		0				0		0			
Max	0		0				0		0			
Pain intensity (Question 4)	0	0.0%	0	0.0%	0.0000	0.00	0	0.0%	0	0.0%	0.0000	0.00
Mean	0.00		0.00		0.0000	0.00	0.00		0.00		0.0000	0.00
SD	0.00		0.00				0.00		0.00			
Median	0		0		0.0000		0		0		0.0000	
Q1	0		0				0		0			
Q3	0		0				0		0			
Min	0		0				0		0			
Max	0		0				0		0			
Pain intensity (Question 5)	0	0.0%	0	0.0%	0.0000	0.00	0	0.0%	0	0.0%	0.0000	0.00
Mean	0.00		0.00		0.0000	0.00	0.00		0.00		0.0000	0.00
SD	0.00		0.00				0.00		0.00			
Median	0		0		0.0000		0		0		0.0000	
Q1	0		0				0		0			
Q3	0		0				0		0			
Min	0		0				0		0			
Max	0		0				0		0			
Pain intensity (Question 6)	0	0.0%	0	0.0%	0.0000	0.00	0	0.0%	0	0.0%	0.0000	0.00
Mean	0.00		0.00		0.0000	0.00	0.00		0.00		0.0000	0.00
SD	0.00		0.00				0.00		0.00			
Median	0		0		0.0000		0		0		0.0000	
Q1	0		0				0		0			

Measures	Unadjusted						After SMRW					
	Roctavian Cohort N=		SoC Cohort N=		p-value (Roctavian vs. SoC)	Std. Diff. (Roctavian vs. SoC)	Roctavian Cohort N=		SoC Cohort N=		p-value (Roctavian vs. SoC)	Std. Diff. (Roctavian vs. SoC)
	N	(%)	N	(%)			N	(%)	N	(%)		
Q3	0		0				0		0			
Min	0		0				0		0			
Max	0		0				0		0			
Pain interference (Question 9)	0	0.0%	0	0.0%	0.0000	0.00	0	0.0%	0	0.0%	0.0000	0.00
Mean	0.00		0.00		0.0000	0.00	0.00		0.00		0.0000	0.00
SD	0.00		0.00				0.00		0.00			
Median	0		0		0.0000		0		0		0.0000	
Q1	0		0				0		0			
Q3	0		0				0		0			
Min	0		0				0		0			
Max	0		0				0		0			
Follow-Up												
Length of follow-up	0	0.0%	0	0.0%	0.0000	0.00	0	0.0%	0	0.0%	0.0000	0.00
Mean	0.00		0.00		0.0000	0.00	0.00		0.00		0.0000	0.00
SD	0.00		0.00				0.00		0.00			
Median	0		0		0.0000		0		0		0.0000	
Q1	0		0				0		0			
Q3	0		0				0		0			
Min	0		0				0		0			
Max	0		0				0		0			
Pain intensity (Question 3)	0	0.0%	0	0.0%	0.0000	0.00	0	0.0%	0	0.0%	0.0000	0.00
Mean	0.00		0.00		0.0000	0.00	0.00		0.00		0.0000	0.00
SD	0.00		0.00				0.00		0.00			
Median	0		0		0.0000		0		0		0.0000	
Q1	0		0				0		0			
Q3	0		0				0		0			
Min	0		0				0		0			
Max	0		0				0		0			
Pain intensity (Question 4)	0	0.0%	0	0.0%	0.0000	0.00	0	0.0%	0	0.0%	0.0000	0.00
Mean	0.00		0.00		0.0000	0.00	0.00		0.00		0.0000	0.00

Measures	Unadjusted						After SMRW					
	Roctavian Cohort N=		SoC Cohort N=		p-value (Roctavian vs. SoC)	Std. Diff. (Roctavian vs. SoC)	Roctavian Cohort N=		SoC Cohort N=		p-value (Roctavian vs. SoC)	Std. Diff. (Roctavian vs. SoC)
	N	(%)	N	(%)			N	(%)	N	(%)		
SD	0.00		0.00				0.00		0.00			
Median	0		0		0.0000		0		0		0.0000	
Q1	0		0				0		0			
Q3	0		0				0		0			
Min	0		0				0		0			
Max	0		0				0		0			
Pain intensity (Question 5)	0	0.0%	0	0.0%	0.0000	0.00	0	0.0%	0	0.0%	0.0000	0.00
Mean	0.00		0.00		0.0000	0.00	0.00		0.00		0.0000	0.00
SD	0.00		0.00				0.00		0.00			
Median	0		0		0.0000		0		0		0.0000	
Q1	0		0				0		0			
Q3	0		0				0		0			
Min	0		0				0		0			
Max	0		0				0		0			
Pain intensity (Question 6)	0	0.0%	0	0.0%	0.0000	0.00	0	0.0%	0	0.0%	0.0000	0.00
Mean	0.00		0.00		0.0000	0.00	0.00		0.00		0.0000	0.00
SD	0.00		0.00				0.00		0.00			
Median	0		0		0.0000		0		0		0.0000	
Q1	0		0				0		0			
Q3	0		0				0		0			
Min	0		0				0		0			
Max	0		0				0		0			
Pain interference (Question 9)	0	0.0%	0	0.0%	0.0000	0.00	0	0.0%	0	0.0%	0.0000	0.00
Mean	0.00		0.00		0.0000	0.00	0.00		0.00		0.0000	0.00
SD	0.00		0.00				0.00		0.00			
Median	0		0		0.0000		0		0		0.0000	
Q1	0		0				0		0			
Q3	0		0				0		0			
Min	0		0				0		0			
Max	0		0				0		0			

Measures	Unadjusted						After SMRW					
	Roctavian Cohort N=		SoC Cohort N=		p-value (Roctavian vs. SoC)	Std. Diff. (Roctavian vs. SoC)	Roctavian Cohort N=		SoC Cohort N=		p-value (Roctavian vs. SoC)	Std. Diff. (Roctavian vs. SoC)
	N	(%)	N	(%)			N	(%)	N	(%)		
Change from Follow-Up												
Pain intensity (Question 3)	0	0.0%	0	0.0%	0.0000	0.00	0	0.0%	0	0.0%	0.0000	0.00
Mean	0.00		0.00		0.0000	0.00	0.00		0.00		0.0000	0.00
SD	0.00		0.00				0.00		0.00			
Median	0		0		0.0000		0		0		0.0000	
Q1	0		0				0		0			
Q3	0		0				0		0			
Min	0		0				0		0			
Max	0		0				0		0			
Pain intensity (Question 4)	0	0.0%	0	0.0%	0.0000	0.00	0	0.0%	0	0.0%	0.0000	0.00
Mean	0.00		0.00		0.0000	0.00	0.00		0.00		0.0000	0.00
SD	0.00		0.00				0.00		0.00			
Median	0		0		0.0000		0		0		0.0000	
Q1	0		0				0		0			
Q3	0		0				0		0			
Min	0		0				0		0			
Max	0		0				0		0			
Pain intensity (Question 5)	0	0.0%	0	0.0%	0.0000	0.00	0	0.0%	0	0.0%	0.0000	0.00
Mean	0.00		0.00		0.0000	0.00	0.00		0.00		0.0000	0.00
SD	0.00		0.00				0.00		0.00			
Median	0		0		0.0000		0		0		0.0000	
Q1	0		0				0		0			
Q3	0		0				0		0			
Min	0		0				0		0			
Max	0		0				0		0			
Pain intensity (Question 6)	0	0.0%	0	0.0%	0.0000	0.00	0	0.0%	0	0.0%	0.0000	0.00
Mean	0.00		0.00		0.0000	0.00	0.00		0.00		0.0000	0.00
SD	0.00		0.00				0.00		0.00			
Median	0		0		0.0000		0		0		0.0000	
Q1	0		0				0		0			
Q3	0		0				0		0			
Min	0		0				0		0			

Measures	Unadjusted						After SMRW					
	Roctavian Cohort		SoC Cohort		p-value (Roctavian vs. SoC)	Std. Diff. (Roctavian vs. SoC)	Roctavian Cohort		SoC Cohort		p-value (Roctavian vs. SoC)	Std. Diff. (Roctavian vs. SoC)
	N=		N=				N=		N=			
	N	(%)	N	(%)			N	(%)	N	(%)		
Max	0		0				0		0			
Pain interference (Question 9)	0	0.0%	0	0.0%	0.0000	0.00	0	0.0%	0	0.0%	0.0000	0.00
Mean	0.00		0.00		0.0000	0.00	0.00		0.00		0.0000	0.00
SD	0.00		0.00				0.00		0.00			
Median	0		0		0.0000		0		0		0.0000	
Q1	0		0				0		0			
Q3	0		0				0		0			
Min	0		0				0		0			
Max	0		0				0		0			

Data source: DHR from Q1 2023 to Q3 2028
Acronyms: SoC: standard of care; COA: clinical outcome assessment; BPI-sf: Brief Pain Inventory - short form; SD: standard deviation
Note: Std. diff. examines the balance of covariate distribution between groups, with a value >0.1 indicating some imbalance between groups and >0.25 indicating poor balance.

Table 13 SMRW-Adjusted COA Linear Mixed Models, Roctavian and SoC Cohorts

HJHS General Linear Mixed Model, Unadjusted

Measures	Estimate	Standard Error	95% Confidence Limits		p-value
			Lower Limit	Upper Limit	
Treatment (Roctavian vs. SoC)	0.00	0.00	0.00	0.00	0.0000
Time					
Time point 1	0.00	0.00	0.00	0.00	0.0000
Time point 2	0.00	0.00	0.00	0.00	0.0000
Time point 3	0.00	0.00	0.00	0.00	0.0000
Treatment by time interaction					
Treatment*time 1	0.00	0.00	0.00	0.00	0.0000
Treatment*time 2	0.00	0.00	0.00	0.00	0.0000
Treatment*time 3	0.00	0.00	0.00	0.00	0.0000

HJHS General Linear Mixed Model, Adjusted

Measures	Estimate	Standard Error	95% Confidence Limits		p-value
			Lower Limit	Upper Limit	
Treatment (Roctavian vs. SoC)	0.00	0.00	0.00	0.00	0.0000
Time					
Time point 1	0.00	0.00	0.00	0.00	0.0000
Time point 2	0.00	0.00	0.00	0.00	0.0000
Time point 3	0.00	0.00	0.00	0.00	0.0000
Treatment by time interaction					
Treatment*time 1	0.00	0.00	0.00	0.00	0.0000
Treatment*time 2	0.00	0.00	0.00	0.00	0.0000
Treatment*time 3	0.00	0.00	0.00	0.00	0.0000

Haemo-QoL-A General Linear Mixed Model, Unadjusted

Measures	Estimate	Standard Error	95% Confidence Limits		p-value
			Lower Limit	Upper Limit	
Treatment (Roctavian vs. SoC)	0.00	0.00	0.00	0.00	0.0000
Time					
Time point 1	0.00	0.00	0.00	0.00	0.0000
Time point 2	0.00	0.00	0.00	0.00	0.0000
Time point 3	0.00	0.00	0.00	0.00	0.0000
Treatment by time interaction					
Treatment*time 1	0.00	0.00	0.00	0.00	0.0000
Treatment*time 2	0.00	0.00	0.00	0.00	0.0000
Treatment*time 3	0.00	0.00	0.00	0.00	0.0000

Haemo-QoL-A General Linear Mixed Model, Adjusted

Measures	Estimate	Standard Error	95% Confidence Limits		p-value
			Lower Limit	Upper Limit	
Treatment (Roctavian vs. SoC)	0.00	0.00	0.00	0.00	0.0000
Time					
Time point 1	0.00	0.00	0.00	0.00	0.0000
Time point 2	0.00	0.00	0.00	0.00	0.0000
Time point 3	0.00	0.00	0.00	0.00	0.0000
Treatment by time interaction					
Treatment*time 1	0.00	0.00	0.00	0.00	0.0000
Treatment*time 2	0.00	0.00	0.00	0.00	0.0000
Treatment*time 3	0.00	0.00	0.00	0.00	0.0000

BPI-sf General Linear Mixed Model, Unadjusted

Measures	Estimate	Standard Error	95% Confidence Limits		p-value
			Lower Limit	Upper Limit	
Treatment (Roctavian vs. SoC)	0.00	0.00	0.00	0.00	0.0000
Time					
Time point 1	0.00	0.00	0.00	0.00	0.0000
Time point 2	0.00	0.00	0.00	0.00	0.0000
Time point 3	0.00	0.00	0.00	0.00	0.0000
Treatment by time interaction					
Treatment*time 1	0.00	0.00	0.00	0.00	0.0000
Treatment*time 2	0.00	0.00	0.00	0.00	0.0000
Treatment*time 3	0.00	0.00	0.00	0.00	0.0000

BPI-sf General Linear Mixed Model, Adjusted

Measures	Estimate	Standard Error	95% Confidence Limits		p-value
			Lower Limit	Upper Limit	
Treatment (Roctavian vs. SoC)	0.00	0.00	0.00	0.00	0.0000
Time					
Time point 1	0.00	0.00	0.00	0.00	0.0000
Time point 2	0.00	0.00	0.00	0.00	0.0000
Time point 3	0.00	0.00	0.00	0.00	0.0000
Treatment by time interaction					
Treatment*time 1	0.00	0.00	0.00	0.00	0.0000
Treatment*time 2	0.00	0.00	0.00	0.00	0.0000
Treatment*time 3	0.00	0.00	0.00	0.00	0.0000

Data source: DHR from Q1 2023 to Q3 2028
Acronyms: COA: clinical outcome assessment; SoC: standard of care; HJHS: Hemophilia Joint Health Score; BPI-sf: Brief Pain Inventory – short form

Table 14 BPI-sf Responder Analysis

Responder Analysis - Patients with ≥15% improvement in BPI-sf scores

Measures	Unadjusted					After SMRW				
	Roctavian Cohort		SoC Cohort		p-value (Roctavian vs. SoC)	Roctavian Cohort		SoC Cohort		p-value (Roctavian vs. SoC)
	N=		N=			N=		N=		
	N	(%)	N	(%)		N	(%)	N	(%)	
Pain intensity (Question 3)	0	0.0%	0	0.0%	0.0000	0	0.0%	0	0.0%	0.0000
Pain intensity (Question 4)	0	0.0%	0	0.0%	0.0000	0	0.0%	0	0.0%	0.0000
Pain intensity (Question 5)	0	0.0%	0	0.0%	0.0000	0	0.0%	0	0.0%	0.0000
Pain intensity (Question 6)	0	0.0%	0	0.0%	0.0000	0	0.0%	0	0.0%	0.0000
Pain interference (Question 9)	0	0.0%	0	0.0%	0.0000	0	0.0%	0	0.0%	0.0000

Responder Analysis - Patients with ≥15% deterioration in BPI-sf scores

Measures	Unadjusted					After SMRW				
	Roctavian Cohort		SoC Cohort		p-value (Roctavian vs. SoC)	Roctavian Cohort		SoC Cohort		p-value (Roctavian vs. SoC)
	N=		N=			N=		N=		
	N	(%)	N	(%)		N	(%)	N	(%)	
Pain intensity (Question 3)	0	0.0%	0	0.0%	0.0000	0	0.0%	0	0.0%	0.0000
Pain intensity (Question 4)	0	0.0%	0	0.0%	0.0000	0	0.0%	0	0.0%	0.0000
Pain intensity (Question 5)	0	0.0%	0	0.0%	0.0000	0	0.0%	0	0.0%	0.0000
Pain intensity (Question 6)	0	0.0%	0	0.0%	0.0000	0	0.0%	0	0.0%	0.0000
Pain interference (Question 9)	0	0.0%	0	0.0%	0.0000	0	0.0%	0	0.0%	0.0000

Data source: DHR from Q1 2023 to Q3 2028
Acronyms: BPI-sf: Brief Pain Inventory – short form

Table 15 Safety Outcomes for Roctavian and SoC Cohorts

Measures	Unadjusted						After SMRW					
	Roctavian Cohort N=		SoC Cohort N=		p-value (Roctavian vs. SoC)	Std. Diff. (Roctavian vs. SoC)	Roctavian Cohort N=		SoC Cohort N=		p-value (Roctavian vs. SoC)	Std. Diff. (Roctavian vs. SoC)
	N	(%)	N	(%)			N	(%)	N	(%)		
All-cause death	0	0.0%	0	0.0%	0.0000	0.00	0	0.0%	0	0.0%	0.0000	0.00
Incidence rate	0.00		0.00		0.0000	0.00	0.00		0.00		0.0000	0.00
Hemophilia-related death	0	0.0%	0	0.0%	0.0000	0.00	0	0.0%	0	0.0%	0.0000	0.00
Incidence rate	0.00		0.00		0.0000	0.00	0.00		0.00		0.0000	0.00
AEs leading to hospitalization	0	0.0%	0	0.0%	0.0000	0.00	0	0.0%	0	0.0%	0.0000	0.00
Event rate	0.00		0.00		0.0000	0.00	0.00		0.00		0.0000	0.00
AEs leading to death	0	0.0%	0	0.0%	0.0000	0.00	0	0.0%	0	0.0%	0.0000	0.00
Incidence rate	0.00		0.00		0.0000	0.00	0.00		0.00		0.0000	0.00
Development of FVIII inhibitors	0	0.0%	0	0.0%	0.0000	0.00	0	0.0%	0	0.0%	0.0000	0.00
Event rate	0.00		0.00		0.0000	0.00	0.00		0.00		0.0000	0.00
Thromboembolic events	0	0.0%	0	0.0%	0.0000	0.00	0	0.0%	0	0.0%	0.0000	0.00
Event rate	0.00		0.00		0.0000	0.00	0.00		0.00		0.0000	0.00
New malignant neoplasms	0	0.0%	0	0.0%	0.0000	0.00	0	0.0%	0	0.0%	0.0000	0.00
Event rate	0.00		0.00		0.0000	0.00	0.00		0.00		0.0000	0.00
Severe liver disease	0	0.0%	0	0.0%	0.0000	0.00	0	0.0%	0	0.0%	0.0000	0.00
Event rate	0.00		0.00		0.0000	0.00	0.00		0.00		0.0000	0.00

Data source: DHR from Q1 2023 to Q3 2028
Acronyms: SoC: standard of care; AE: adverse event; FVIII: coagulation factor VIII
Note: Event rates will be calculated for events that may happen multiple times per person, while incidence rates will be calculated for events that only happen once per person.
Note: Event rates will be calculated as the number of events per 100 person-years: (number of events in each cohort during the overall follow-up period / total number of years in each cohort during the follow-up period) * 100
Note: Incidence rate will be calculated as the number of new events per 100 person-years: (number of new events in each cohort during the overall follow-up period / total number of years in each cohort during the follow-up period) * 100

Note: Std. diff. examines the balance of covariate distribution between groups, with a value >0.1 indicating some imbalance between groups and >0.25 indicating poor balance.
Note: The treatment policy estimand will be applied as necessary to check the robustness of the results and for outcomes where the hypothetical estimand is warranted (e.g., comparisons of safety).

Table 16 Time to Resumption of Prophylactic Treatment for Roctavian Cohort

Measures	Roctavian Cohort	
	N=	
	N	(%)
Patients who resumed prophylactic treatment	0	0.0%
Time to resumption of prophylactic treatment (days)		
Mean	0.00	
SD	0.00	
Median	0	
Q1	0	
Q3	0	
Min	0	
Max	0	

Data source: DHR from Q1 2023 to Q3 2028
Acronyms: SD: standard deviation

Figure 1 Histograms of ABR for Roctavian and SoC Cohorts

12.2. Haemo-QoL-A Scoring

Haemo-QoL-A

The following questions ask how hemophilia and its treatment affect your life. Please take your time and answer all of the questions. There are no right or wrong answers. Please read each question carefully and select one response for each question. If you are unsure about how to answer a question, choose the one response that best represents your opinion.

The first set of questions asks about how **hemophilia** affects your **day-to-day activities**. Think about the **past 4 weeks** when answering these questions.

Please circle the best answer:

		None of the time	A little of the time	Some of the time	A good bit of the time	Most of the time	All of the time
1.	Loss of joint mobility affects how I walk.	0	1	2	3	4	5
2.	It is hard for me to climb the stairs.	0	1	2	3	4	5
3.	It is *easy* for me to perform daily activities.	0	1	2	3	4	5
4.	I am unable to leave the house because of my hemophilia.	0	1	2	3	4	5
5.	I have to adjust my activities because of pain.	0	1	2	3	4	5
6.	I am *able* to complete household tasks.	0	1	2	3	4	5
7.	It is *easy* for me to lift heavy objects.	0	1	2	3	4	5
8.	I depend on others to carry out activities around the home.	0	1	2	3	4	5
9.	I am *able* to participate in sports.	0	1	2	3	4	5
10	I have difficulty traveling because of my hemophilia.	0	1	2	3	4	5
11.	I am afraid of being far from a health care center with emergency care facilities.	0	1	2	3	4	5

Please continue ☞

The next set of questions asks about how **hemophilia** affects your **mood and feelings**. Think about the **past 4 weeks** when answering these questions.

Please circle the best answer:

		None of the time	A little of the time	Some of the time	A good bit of the time	Most of the time	All of the time
12.	I am hopeful about the future.	0	1	2	3	4	5
13.	I worry about accidents.	0	1	2	3	4	5
14.	I am afraid of being hit or bumped.	0	1	2	3	4	5
15.	I feel less confident than others.	0	1	2	3	4	5
16.	I enjoy life.	0	1	2	3	4	5
17.	I feel much older than my years.	0	1	2	3	4	5
18.	I am afraid of internal bleeding.	0	1	2	3	4	5
19.	I am in control of my life.	0	1	2	3	4	5
20.	I feel like I'm taking a risk when I do things	0	1	2	3	4	5
21.	I feel frustrated because I can't do what I want to do.	0	1	2	3	4	5
22.	Because of my hemophilia, I have difficulty planning for the future.	0 5	1 4	2 3	3 2	4 1	5 0

Please continue ☞

Now we would like to ask you about how **hemophilia** affects your **work or school life, family life and social life**. Think about the **past 4 weeks** when answering these questions.

Please circle the best answer:

		None of the time	A little of the time	Some of the time	A good bit of the time	Most of the time	All of the time
23.	I worry about finding or losing a job.	0	1	2	3	4	5
24.	I worry about missing work or school because of my hemophilia.	0	1	2	3	4	5
25.	I experience restrictions at work or school.	0	1	2	3	4	5
26.	I feel like a burden to my family.	0	1	2	3	4	5
27.	I worry about having children.	0	1	2	3	4	5
28.	Hemophilia interferes with my relationships with my friends.	0	1	2	3	4	5
29.	I worry about not being able to provide for my family.	0	1	2	3	4	5
30.	I am afraid to go to crowded places like concerts or bars for fear of being bumped or injured.	0	1	2	3	4	5
31.	I feel different from others because of my hemophilia.	0	1	2	3	4	5
32.	I feel I have the same opportunities to succeed in life as others.	0	1	2	3	4	5
33.	Others treat me differently.	0	1	2	3	4	5
34.	I feel I can carry out a normal life like the rest of society.	0	1	2	3	4	5
35.	Hemophilia interferes with my ability to have an intimate relationship with another person.	0	1	2	3	4	5
36.	I am afraid of having a bleed in public.	0	1	2	3	4	5

Please continue ☞

The following questions ask about your experiences with your **hemophilia treatment**. Think about the **past 4 weeks** when answering these questions.

Please circle the best answer:

		None of the time	A little of the time	Some of the time	A good bit of the time	Most of the time	All of the time
37.	My hemophilia treatment interferes with my daily activities.	0	1	2	3	4	5
38.	My infusions for hemophilia are stressful.	0	1	2	3	4	5
39.	I worry about the safety of my treatment.	0	1	2	3	4	5
40.	I worry about being treated by health care providers who do not know how to treat hemophilia.	0	1	2	3	4	5
41.	I worry about the availability of hemophilia products.	0	1	2	3	4	5

SCORING MANUAL FOR THE HAEMO-QOL-A

Items are answered on a 6-point Likert-type scale, ranging from 0 (None of the time) to 5 (All of the time). Higher scores mean better HRQL or less impairment for a particular subscale.

Recoding items
Some items are positively worded and some are negatively worded. Negatively worded items should be reverse scored so that higher scores reflect better quality of life. The item scores of negatively worded items should be subtracted from 5. For example: Question 1 is a negatively worded item so it should be scored:

(5 – Question 1) = score of reverse scored Question 1.

The positively worded items are the following: 3, 6, 7, 9, 12, 16, 19, 32, and 34. All other items are negative and should be reverse scored.

Scoring

For the Haemo-QoL-A subscales [physical functioning, role functioning, worry, consequences of bleeding, emotional impact (formerly: positive affect), treatment concern], scores are computed by averaging across the items within a subscale. The range of subscale scores is 0 to 5; higher scores mean better HRQL or less impairment for a particular subscale.

To calculate the Haemo-QoL-A total score, sum the value of the individual subscales (do not sum all the individual items). The range of total scores is 0 to 30; higher scores mean better HRQL or less impairment.

For both total and subscale scores, use the formula below to transform raw scores to a 0 to 100 scale. Higher scores will be indicative of better HRQL.

Missing Items
For the subscale analyses, if < 50% of the scale items are missing, the scale should be retained with the mean scale score of the items present used to impute a score for the missing items. If $\geq$ 50% of the items are missing, no scale score should be calculated, the subscale score should be considered missing. If a subscale score is missing, the Haemo-QoL-A total score cannot be calculated

Items by subscale:

SAS Variable Name	Number	Scoring
Physical Functioning		
rHQ3	1	Reverse
rHQ4	2	Reverse
HQ5	3	
rHQ7	5	Reverse
HQ8	6	
HQ9	7	
rHQ10	8	Reverse
HQ12	9	
rHQ14	10	Reverse
Role Functioning		
rHQ6	4	Reverse
rHQ21	17	Reverse
rHQ25	21	Reverse
rHQ26	22	Reverse
rHQ31	26	Reverse
rHQ33	28	Reverse
rHQ37	31	Reverse
rHQ39	33	Reverse
rHQ45	36	Reverse
rHQ46	37	Reverse
rHQ48	38	Reverse
Worry		
rHQ28	23	Reverse
rHQ29	24	Reverse
rHQ30	25	Reverse
rHQ32	27	Reverse
rHQ34	29	Reverse
Consequences of Bleeding		
rHQ15	11	Reverse
rHQ17	13	Reverse
rHQ18	14	Reverse
rHQ19	15	Reverse
rHQ22	18	Reverse

rHQ24	20	Reverse
rHQ36	30	Reverse
Emotional Impact		
HQ16	12	
HQ20	16	
HQ23	19	
HQ38	32	
HQ43	34	
rHQ44	35	Reverse
Treatment Concern		
rHQ49	39	Reverse
rHQ51	40	Reverse
rHQ52	41	Reverse

Scale	Average the Item Values	Lowest/Highest Possible Raw Scores	Range
Physical functioning	$\frac{(1+2+3+5+6+7+8+9+10)}{9}$	0, 5	5
Role functioning	$\frac{(4+17+21+22+26+28+31+33+36+37+38)}{11}$	0, 5	5
Worry	$\frac{(23+24+25+27+29)}{5}$	0, 5	5
Consequences of bleeding	$\frac{(11+13+14+15+18+20+30)}{7}$	0, 5	5
Emotional impact	$\frac{(12+16+19+32+34+35)}{6}$	0, 5	5
Treatment concern	$\frac{(39+40+41)}{3}$	0, 5	5
Haemo-QoL-A Total	Sum of subscales (not individual items)	0, 30	30

Formula for transformation of the Haemo-QoL-A total raw score:

$$\text{Transformed Score} = \frac{\textit{Actual raw}\text{ total score}}{\text{Possible raw score range}} \times 100$$