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

Protocol Version: 3.0

Protocol Date: 24 June 2024

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INVESTIGATOR AGREEMENT

I have read the attached protocol entitled "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" dated 24 June 2024 and agree to abide by all provisions set forth therein.

I agree to comply with the International Conference on Harmonization Tripartite Guideline on Good Clinical Practice, Good Pharmacovigilance Practice, and all applicable regulations and local guidelines.

I agree to ensure that the confidential information contained in this document will not be used for any purpose other than the evaluation or conduct of the study without the prior written consent of BioMarin.

I agree to ensure that Financial Disclosure Statements will be completed by:

- me (including, if applicable, my spouse [or legal partner] and dependent children)
- my sub-investigators (including, if applicable, their spouse [or legal partner] and dependent children)

at the start of the study and for up to 1 year after the study is completed, if there are changes that affect my financial disclosure status.

_____

Investigator Signature Date (DD-MMM-YYYY)

Printed name: _____

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>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 people with severe hemophilia A (PwSHA).
The study objectives and endpoints below will compare Roctavian and SoC prophylaxis treatment with exogenous coagulation factor VIII (FVIII) or emicizumab, unless otherwise noted.</td></tr>
<tr><td></td><td>Objectives</td><td>Endpoints</td></tr>
<tr><td></td><td colspan="2">Primary:</td></tr>
<tr><td></td><td>To compare the annualized bleeding rate for treated bleeds.</td><td>• Bleeding events requiring treatment with exogenous coagulation FVIII.</td></tr>
<tr><td></td><td colspan="2">Secondary:</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.
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<tr><td></td><td>To compare the proportion of people with zero bleeds for treated, major, life threating, and joint bleeds.</td><td>• Bleeding events requiring treatment with exogenous FVIII.
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<tr><td></td><td>To compare the use of hemostatic medications.</td><td>• Prophylactic hemostatic treatments.
• On-demand hemostatic treatments.</td></tr>
</table>

	To compare joint health, quality of life, and pain.	• Hemophilia joint health score (HJHS). • Haemo-Quality of Life assessment (QoL-A). • 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 persons 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 Cohort.	
Medicinal Products	Roctavian. Hemostatic prophylaxis treatments: FVIII replacement therapies or emicizumab.	
Summary of Eligibility Criteria	Adult (≥18 years old) male PwSHA registered in the German Hemophilia Register (DHR) database administered Roctavian or hemostatic prophylaxis during the study recruitment period with FVIII or emicizumab with no history of (or current) FVIII inhibitors, no acute infections (such as acute respiratory infections or acute hepatitis) or uncontrolled chronic infections (such as chronic active hepatitis B), and/or no known significant hepatic fibrosis or cirrhosis.	

Data Elements of Interest	Key data elements to compare or describe outcomes in the Roctavian Cohort and SoC Cohort 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 Cohort and SoC Cohort 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
ATE	average treatment effect
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
DHG	Deutsche Hämophiliegesellschaft zur Bekämpfung von Blutungskrankheiten e. V.
DHR	German Hemophilia Register, *Deutsches Hämophilieregister*
EHL	extended half- life
FVIII	coagulation factor VIII
FVIII-SQ	human coagulation factor VIII with 14 amino acid long (SQ) linker sequence
G-BA	Federal Joint Committee
GTH	Gesellschaft für Thrombose- und Hämostaseforschung e. V.
HA	hemophilia A
HCP	health care practitioners
HCV	hepatitis C Virus
hFVIII	human coagulation factor VIII
hFVIII-SQ	hFVIII gene linker sequence
HJHS	Hemophilia Joint Health Score
HTC	Hemophilia Treatment Center
ICF	informed consent form
IEC	independent ethics committee
IgG	immunoglobulin G

Abbreviation	Definition
IGH	Interessengemeinschaft Hämophiler e. V.
IPTW	inverse probability of treatment weight
IQWiG	Institute for Quality and Efficiency in Health Care
IRB	institutional review board
ITT	immune tolerance therapy
IU	international units
MCID	minimal clinically important differences
PD	plasma-derived
PEG	polyethylene glycol
PRO	patient-reported outcome
PS	propensity score
PSM	propensity score matching
PwHA	person/people with hemophilia A
PwSHA	person/people with severe hemophilia A
QoL-A	quality of life assessment
REB	research ethics board
RR	risk ratio
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SHL	standard half- life
SMD	standardized mean difference
SmPC	Summary of Product Characteristics
SMRW	standardized mortality ratio weighting
SoC	standard of care
TFG	Transfusion Act

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 2007). 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 supplementation 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 (Miesbach 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 medicinal products 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).

3.2. Routine Data Collection and Evaluations for Valoctocogene Roxaparvovec

3.2.1. 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 für 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).

3.2.2. Compared Therapies

3.2.2.1. ROCTAVIAN®

Valoctocogene 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.

3.2.2.2. Factor VIII substitution

FVIII concentrates derived from human plasma or manufactured by recombinant technologies in cell culture can be used for hemostatic prophylaxis. The half-life of FVIII in plasma is 10 to 12 hours. Therefore, it is necessary to inject plasma-derived or standard half-live FVIII concentrates at least 3 times per week. Factor VIII 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).

3.2.2.3. 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).

3.3. Rationale

This study is being undertaken to fulfill the G-BA requirement for Routine Data Collection and Evaluations (as described in Section 3.2.1). Specifically, this study will provide data on the comparative effectiveness of Roctavian to Standard of Care (SoC) hemostatic prophylaxis treatments (see Section 3.2.2.2 and Section 3.2.2.3) among people with severe HA (PwSHA) without a history of (or current) 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 exogenous 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 people 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 persons administered Roctavian.	• Resumption of prophylactic hemostatic treatments

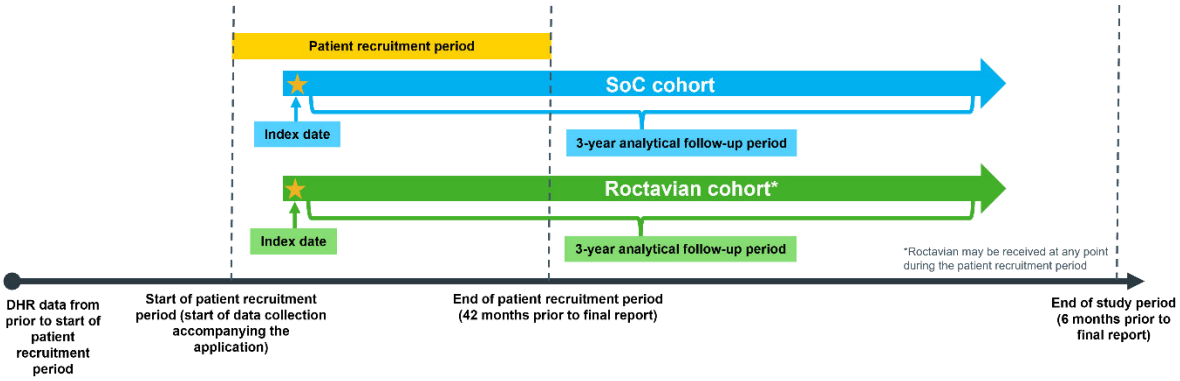
5. STUDY METHODS

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 exogenous 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 per 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 recruitment period beginning approximately 3 months after this protocol is agreed with the G-BA (to allow for ethics committee approval of the final protocol) and ending in approximately 42 months prior to the date of the final report required by the G-BA resolution for the AbD. This study recruitment 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.

Participants will be assigned to a study cohort based on the treatment that was received during the recruitment period. All participants receiving Roctavian during the recruitment period will be assigned to the Roctavian Cohort. Participants receiving SoC hemostatic prophylaxis treatment only during the recruitment period 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 consents to the AbD while on SoC and subsequently receives Roctavian during the recruitment period, inclusion/exclusion will be reassessed at the time of Roctavian administration. For these participants, baseline assessments, including patient reported outcome measures, will also be re-assessed at the time of Roctavian administration. If a participant in the SoC Cohort subsequently receives Roctavian during follow-up after the recruitment period, their data will be censored for analysis (censoring discussed further in Section 10.3). Study participants will be followed consistent with the Study Elements of Interest (see Section 7.1) from index through the follow-up period. 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 approximately 6 months prior to the final report required to be submitted to G-BA. Figure 2 illustrates the overall study conduct. The study completion date is based on allowing time to analyze data and submit a final report on the AbD defined by the G-BA resolution . Changes to the AbD defined deadlines for the final report would result in changes to the study completion timeframe, as well as the recruitment window described above.

Figure 1: Study Schema



The Roctavian Cohort and SoC Cohort 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 (HTC) every 6 months and therefore it is expected that clinical outcome assessments of quality of life and pain would be assessed at those timepoints, with joint health assessed at least annually. Comparisons of safety will also be conducted. 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 Cohort and SoC Cohort 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. A study schema illustrating differing estimands of comparative effectiveness are presented in Section 10.3.

5.2. Study Population

Data for adult PwSHA and without a history of (or current) 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 (exogenous FVIII replacement treatments or emicizumab). Approximately 70 PwSHA and 330 PwSHA are expected to be enrolled in the Roctavian Cohort and SoC Cohort, 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 clinical 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 eligibility criteria for participation in the study are provided in Section 5.2.1 and Section 5.2.2. Eligibility criteria will be confirmed at time of enrollment based on DHR field that the participant fulfills the AbD inclusion/exclusion criteria.

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 recruitment window
  - Participant administered commercially available Roctavian. Note: Assignment of a therapeutic strategy is not determined by this protocol.

  OR

  - Has received prophylactic treatment with exogenous FVIII or emicizumab
- Participant (or their legally authorized representative, if appropriate) has provided written, signed informed consent for participation in the study

5.2.2. Exclusion Criteria

Individuals 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
- Presence of acute infections (such as acute respiratory infections or acute hepatitis) or uncontrolled chronic infections (such as chronic active hepatitis B), and/or known significant hepatic fibrosis or cirrhosis at index

6. PARTICIPANT ENROLLMENT

Before participants 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 participant information and/or recruitment material, if applicable. All participants, or their legally authorized representative (if applicable), must sign and personally date the consent form before the collection of any study specific data. All participants who enter the study will be assigned a unique participants identification number.

This number will be used to identify the participant throughout the study and must be used on all study documentation related to that participant (where applicable/appropriate).

Participants are considered enrolled when they have signed the consent for this study. They must also have previously signed the consent for recording their data in the DHR.

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 (Roctavian/SoC) 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). Per existing local regulations, data can be reported into the DHR based on all data for a site or at an individual participant level. Inherent to consenting to the AbD and the data entry needed for this study, data will be entered at an individual level for all AbD participants.

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 participant 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 each participants 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 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. All data fields in Sections 7.2.3, 7.2.4, and 7.2.5 are mandatory to compete for individuals who consents to participate in this data collection. Data fields in the DHR (described in Sections 7.2.3, 7.2.4, and 7.2.5) are either mandatory to be entered into the registry per DHR practices or will be monitored (see Section 7.1.2) to ensure completeness of data for analyses.

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		X	X
Gene Therapy Information		X[b]		
AAV Serostatus Testing Information	X	X		
Use of immunosuppression for gene therapy		X[b]	X[b]	
FVIII Activity Levels			X[b]	
Clinical Outcome Assessments				
Haemo-QoL-A questionnaire	During baseline or Index[c]	During baseline or Index[c]	Bi-Annually[d]	At end of study period or participant discontinuation[f]
Hemophilia Joint Health Score (HJHS)	During baseline or Index[c]	During baseline or Index[c]	Annually[e]	At end of study period or participant discontinuation[f]
BPI-SF	During baseline or Index[c]	During baseline or Index[c]	Bi-Annually[d]	At end of study period or participant discontinuation[f]

Variables	Baseline Data (prior to index)	At index	Data entered as observed after index	End of Follow-up (3 years post index)
Safety Information				
Death			X[g]	At participant discontinuation[g]
Hemophilia-related death			X[g]	At participant discontinuation[g]
Adverse events leading to hospitalization[h] or death			X[g]	At end of study period or participant discontinuation[g]
Thromboembolic events			X[g]	At end of study period or participant discontinuation[g]
Severe liver disease (liver failure, liver fibrosis and/or progression of liver fibrosis or cirrhosis			X[g]	At end of study period or participant discontinuation[g]
New malignant neoplasms			X[g]	At end of study period or participant 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.

a Based on data recorded in the DHR for the 12 months prior to index (or portion thereof)

b Recorded for the Roctavian Cohort only

c 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 participant.

d Assessment requested to be completed for all AbD participants entered into the DHR approximately every 6 months relative to the index date during follow-up consistent with routine clinical management of a participant.

e Assessment requested to be completed for all AbD participants entered into the DHR at least every year relative to the index date during follow-up consistent with routine clinical management of a participant.

f 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 participant or at the time of discontinuation.

g Data requested to be entered through the study period including at the end of the study period (approximately 3 years after the index date) or at time of participant discontinuation.

h Hospitalization defined as a participant having been admitted to the hospital for inpatient care, either to the inpatient ward or to the emergency room for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting.

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 PS. 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.

In order to maximize the interpretability of interim analyses, study sites will be asked to enter data specifically for these analyses, which may fall outside of annual reporting at a site (see Section 10.4). Trained site monitors will provide support to participating sites to minimize the incidence of missing data through routine on-site monitoring visits and remote routine monitoring visits, tailored to each site depending on the number of participants enrolled and data entry compliance into the DHR (see Section 11.8).

Furthermore, prior to each planned interim analysis reporting period, site monitors will perform on-site monitoring visits to ensure that all available data has been recorded into the DHR for enrolled participants only.

Data on ongoing events (see Table 6, Table 7, and Table 8) 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 approximately 6 months prior to the final report specified in the G-BA AbD resolution after the last participant 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 participant's 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) and/or initiate participation in a clinical trial, 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).

The German Hemophilia Registry (ie, Deutsches Hämophilieregister [DHR]) 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 individuals 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 in Germany 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 Section 7.2.3 and Section 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). All variables planned to be utilized for the analysis *a priori* are defined in sections below and the SAP. If any additional derived variables or changes to these *a priori* definitions occur during the study conduct, these additional variable or definitions will be recorded 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 participants in 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	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) is collected in DHR, but only year is available for analysis per DHR practices. Inclusion criteria of aged ≥18 years of age at index and confirmed at time of enrollment based on DHR field confirming that the participant fulfills the AbD inclusion/exclusion criteria. 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 participants at index. Ability to collect month or date of birth were discussed with the registry though collection of this potential personally identifiable information are not possible based on DHR practices.
Gender	Male gender	✓	--	At enrollment	Confirm inclusion criteria. Inclusion criteria additionally confirmed at time of enrollment based on DHR field confirming that the participant fulfills the AbD inclusion/exclusion criteria.
Height	Height in cm	✓	At index or during baseline	Ongoing	Description of cohorts, based on recording closest to or at index
Weight	Weight in kg	✓	At index or during baseline; follow-up	Ongoing	Description of cohorts, based on recording closest to or at index Data will additionally be utilized to derive treatment utilization data (see Table 7).

Variable	Description	Captured in DHR	Time period for Analysis	Entry into DHR	Operational notes including Relevant Data Fields in DHR
Body mass index (BMI)	Body mass index in kg/m^2	Derived variable based on captured variables	At index or during baseline	--	Description of cohorts, 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.)
Hemophilia Treatment Center (HTC)	Primary HTC/institution managing a patient	X (see operational note)	At index	Ongoing	N/A HTC primarily managing a participant will be 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; follow-up	Ongoing	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. Exclusion criteria confirmed at time of enrollment based on DHR field confirming that the participant fulfills the AbD inclusion/exclusion criteria. 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 and AAV Status

Variable	Description	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. Inclusion criteria additionally confirmed at time of enrollment based on DHR field confirming that the participant fulfills the AbD inclusion/exclusion criteria.
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 therapy administration	Age of first FVIII administration	✓	--	At enrollment	Description of cohorts Derived based on date of first FVIII therapy 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. Exclusion criteria additionally confirmed at time of enrollment based on DHR field

Variable	Description	Captured in DHR	Time period for Analysis	Entry into DHR	Operational notes including Relevant Data Fields in DHR
					confirming that the participant fulfills the AbD inclusion/exclusion criteria.
von Willebrand Factor	von Willebrand factor level	✓	At index or any time prior to index	At enrollment into the AbD	Potential variable for inclusion in the propensity score, to be determined based on statistical association
Target joints	Presence of target joints	✓	At index and/or during baseline	Ongoing	Description of cohorts. Presence of a target joint will be derived based on therapy usage recorded in the DHR for bleeding with the bleeding location identified as 'target joint'. Number and location of target joints will be based on location (shoulder, elbow, hip, knee, ankle, or other) and side (left, right, not applicable, or unknown) of bleeds identified as 'target joint'. For example, if a target joint bleeds are recoded at the same location on both sides (eg, a target joint bleed at the left ankle and a separate target joint bleed at the right ankle), this will be counted as 2 separate target joints. If the target joint location is 'other joint' or the side of bleeding is 'not applicable or unknown', the number of target joints identified from the bleed will be counted as 1 target joint. 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.

Variable	Description	Captured in DHR	Time period for Analysis	Entry into DHR	Operational notes including Relevant Data Fields in DHR
Treatment History					
Use of prophylaxis	Hemostatic prophylaxis use prior to index	✓	Baseline	Ongoing	Derived based on the therapy usage recorded in the DHR. Inclusion criteria confirmed at time of enrollment based on DHR field confirming that the participant fulfills the AbD inclusion/exclusion criteria.
Prophylaxis type	Medication class utilized for prophylaxis	✓	Baseline	Ongoing	Description of cohorts. 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 cohorts. 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 cohorts. 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).

Variable	Description	Captured in DHR	Time period for Analysis	Entry into DHR	Operational notes including Relevant Data Fields in DHR
AAV Status					
AAV Antibody testing	Serostatus for AAV 5 antibodies	✓	Index	At/around time of administration for Roctavian Cohort Ongoing for any testing done during the study	Derived from AAV testing for AAV5 being conducted and result of positive/negative.
Comorbidities					
Hepatitis C Virus (HCV) status	History of HCV, along with treatment 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 (cured infection vs no infection history) Treatment for HCV eradication during baseline Presence of acute or uncontrolled chronic hepatic infections at index is an exclusion criteria. HCV status as documented in the DHR will be used to describe the population, as well as confirm inclusion/ exclusion criteria. Exclusion criteria will additionally confirmed at time of enrollment based on DHR field confirming that the participant fulfills the AbD inclusion/exclusion criteria.
Chronic liver disease status	Presence of liver fibrosis and/or cirrhosis	✓	Baseline	Ongoing	Description of cohorts. Based on liver disease (eg, report of fibrosis) recorded in the DHR. Presence of known significant hepatic fibrosis or cirrhosis at index is an exclusion criteria, which will be confirmed at time of

Variable	Description	Captured in DHR	Time period for Analysis	Entry into DHR	Operational notes including Relevant Data Fields in DHR
					enrollment based on DHR field confirming that the participant fulfills the AbD inclusion/exclusion criteria. Definitions of acute liver failure (Tholey 2023), liver fibrosis and/or progression of liver fibrosis (Lee 2022a), or cirrhosis (Lee 2022) will be consistent with MSD Manuals for classification. Fibrosis status as documented in the DHR will be used to describe the population.
Other comorbid diseases	History of malignancy, hypertension or osteoporosis	✓	At index, during baseline, and/or any time prior to index	At enrollment into the AbD & Ongoing	Potential variable for inclusion in the propensity score, to be determined based on statistical association. Derived based on prespecified list of comorbid diseases including malignancy, hypertension, and osteoporosis. Malignancies are expected to be defined consistent the safety outcomes (Patel 2020). Hypertension (ie, elevated blood pressure) is expected to be defined as sustained elevation of resting systolic blood pressure (≥ 130 mm Hg), diastolic blood pressure (≥ 80 mm Hg), or both (Bakris 2023). Osteoporosis is expected to be defined as a progressive metabolic bone disease that decreases bone mineral density (bone mass per unit volume), with deterioration of bone structure. Osteoporosis is defined as DXA results for T-scores ≤ -2.5 (Bolster 2023).

AAV, Adeno-associated virus; 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 Roctavian 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 Roctavian 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.

Table 5: Gene Therapy Administration Variables

Variable	Description	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
Use of any immuno-suppression	Use of any immune-suppression	✓	Index and during follow-up	At administration and ongoing	Description of the Roctavian cohort based on any reported used of immunosuppressants (yes/no), as well as immune-suppressant drugs based on the DHR specified list of immunosuppressant medications.
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.

DHR, German Hemophilia Register.

7.2.5. Clinical Outcomes of Interest

The Roctavian Cohort and SoC Cohort 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. Bleeding events will be recorded from the index date through the follow-up period for each participant in the AbD.

Table 6: Bleeding Events

Variable	Description	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 spontaneous 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. Definition of 'severe' and ‘life-threatening’ severity will be consistent with existing practices in the DHR[1].
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. Definition of ‘life-threatening’ severity will be consistent with existing practices in the DHR[1].

Variable	Description	Captured in DHR	Time period for Analysis	Entry into DHR	Operational notes including Relevant Data Fields in DHR
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

[1] Definition confirmed by DHR as consistent with PedNet. A bleed is classified as severe if the bleed causes pain, swelling, and/or mobility disability and does not end within 24 hours. A bleed is classified as life threatening if the bleed is severe (causes pain, swelling, and/or mobility disability and does not end within 24 hours) and poses a special risk to the patient.

7.2.5.2. Use of hemostatic treatments

Endpoints for secondary objectives regarding hemostatic therapy usage will be based on therapeutic usage of exogenous 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 exogenous FVIII or emicizumab, the number of uses (stratified by prophylaxis vs on-demand/for bleed treatment), amount of exogenous 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 starting from index date (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. Hemostatic therapy usage will be recorded from the index date through the follow-up period for each participant in the AbD.

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	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 exogenous 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) and on-demand use. Will be described based on total FVIII utilized in international units (IUs), as well as IU/KG based on weight data (see Table 3). On demand use of FVIII will be defined as use of FVIII for suspected bleeding, spontaneous bleeding, traumatic, bleeding/bleeding, or intensified on-demand treatment (short-term prophylaxis).
Infusion/ Injection Rate	Number of infusions/ injections during follow-up	✓	Follow-up	Ongoing	Derived based on the therapy usage and frequency of use during individual usage periods recorded in the DHR for any reason and summarized as annualized infusion/injection rate (AIR).
Return to prophylaxis	*For Roctavian Cohort only* Use of continuous prophylaxis	✓	Follow-up	Ongoing	Derived based on the recording of physician report of 'return to prophylaxis' in the DHR.

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 Proprietary and Confidential

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 7.2.5.4, 7.2.5.5, and 7.2.5.6, respectively. 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. Physicians participating in the AbD are expected to enter data for these instruments collected relative to the study index date per the data elements of interest (Table 2).

7.2.5.4. 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.

7.2.5.5. 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 participants 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).

7.2.5.6. 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) (Cleland 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 participants to report on the nature of their pain.

7.2.5.7. Safety outcomes

Safety events of interest (all cause death, hemophilia-related death, adverse events leading to hospitalization and/or death, and targeted adverse events of development of FVIII inhibitors, thromboembolic events, new malignant neoplasms, and severe liver disease) will be described for each cohort based on data recorded in the DHR. See Table 8 for detail on events captured and relevant data field when applicable. Safety events will be described and compared based on events recorded starting on the index date and throughout the follow-up period for each participant.

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

Table 8: Safety Events of Interest

Variable	Description	Captured in DHR	Time period for Analysis	Entry into DHR	Operational notes including Relevant Data Fields in DHR
All cause death	Deaths occurring due to any cause	✓	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, non-hemophilia-related, or unknown. (See limitations of interpretation of events regardless of relationship to hemophilia treatment in Section 10.5).
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	Medical event leading to hospitalization and/or death	✓	Follow-up (inclusive of index)	Ongoing	The DHR captures information on medically relevant events including allergic reactions, thromboembolic events, thrombotic microangiopathy, malignant neoplasm, autoimmune disease, sensory paresthesia, infusion/hypersensitivity reaction, complications of immunosuppression 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, along with serious consequences due to the event (hospitalization, death, none or unknown). Event recorded as leading to hospitalization and/or death will be analyzed both for any reason (regardless of relation to hemophilia treatment) and related to hemophilia treatment. (See limitations of interpretation of events regardless of relationship to hemophilia treatment in Section 10.5). Hospitalizations are defined as a participant having been admitted to the hospital for inpatient care, either to the inpatient ward or to the emergency room for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting.

Variable	Description	Captured in DHR	Time period for Analysis	Entry into DHR	Operational notes including Relevant Data Fields in DHR
Targeted Adverse Events					
Development of FVIII inhibitors	Positive inhibitor tests and/or a positive test and the 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 in the DHR 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. (See limitations of interpretation of events regardless of relationship to hemophilia treatment in Section 10.5)
Malignant neoplasms	Occurrence of a malignancy	✓	Follow-up (inclusive of index)	Ongoing	Derived based recording of medically relevant event of malignant neoplasm in the DHR. Malignant neoplasms have cells that grow uncontrollably and spread locally and/or to distant sites. Malignant tumors are cancerous (ie, they invade other sites). They spread to distant sites via the bloodstream or the lymphatic system. This spread is called metastasis. Metastasis can occur anywhere in the body (Patel 2020). Malignancies are expected to be defined consistent with other data collection occurring in the study population, including the International World Federation of Hemophilia Gene Therapy Registry (WFH 2024; Konkle 2020).
Severe liver disease (liver failure, liver fibrosis and/or progression of liver	Occurrence of new severe liver disease	✓	Follow-up (inclusive of index)	Ongoing	Derived based on recording of liver disease status (liver fibrosis (new diagnosis), liver failure, and liver cirrhosis). Occurrence of severe liver disease (liver failure, liver fibrosis and/or progression of liver fibrosis, or cirrhosis). Recording during follow-up of 'liver fibrosis (new diagnosis)' or 'liver failure' will be used to identify events. Progression of fibrosis or cirrhosis will be identified based on recording of an increased Child-Turcotte-Pugh classification (eg, A → B, B→C) of liver disease relative to liver disease status at baseline or the new diagnosis of cirrhosis (Lee 2022; Lee 2022a; Tholey 2023). Definitions of acute liver failure

Variable	Description	Captured in DHR	Time period for Analysis	Entry into DHR	Operational notes including Relevant Data Fields in DHR
fibrosis, or cirrhosis)					(Tholey 2023), liver fibrosis and/or progression of liver fibrosis (Lee 2022a), or cirrhosis (Lee 2022) will be consistent with MSD Manuals for classification. Similar to the description of thromboembolic events, both events regardless of relationship to hemophilia treatment and specifically related to hemophilia treatment will be analyzed. (See limitations of interpretation of events regardless of relationship to hemophilia treatment in Section 10.5). The definition of severe liver disease (acute liver failure, worsening of liver fibrosis, liver cirrhosis) is consistent with other data collection occurring in the study population, including the International World Federation of Hemophilia Gene Therapy Registry (WFH 2024; Konkle 2020).

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 participant who requests to be withdrawn. 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 participant from the study include the following:

- Death
- Lost to follow-up (see Section 8.2)
- Use of any investigational product or investigational medical device during the study
- Participant was erroneously admitted into the study or does not meet entry criteria per Section 5.2.1
- Participant no longer has severe hemophilia A (eg, participant has received liver transplant)

The investigator or designee must explain to each participant, before enrollment into the study, that for the evaluation of study results, the participant's protected health information obtained during the study will be shared with the sponsor, regulatory agencies, and the IRB/IEC/REB. It is the physician'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 participant'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 participant and the participant 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 study site or does not respond to attempts at contact made by the study site. A participant will be deemed lost to follow-up at the discretion of the participant's 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 participants consenting to the AbD data collection during the recruitment 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 study physicians, regulatory authorities, and the IRB/IEC/REB. The study physician is responsible for communicating any decision to terminate the study to hospital/HTC staff involved in the conduct of the study and the participating participants (and/or their legally authorized representative).

8.4.1. Futility Assessment

A futility analysis will be conducted at the 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 participants enrolled in the study, the number of participants in the Roctavian Cohort and SoC Cohort at the time and the amount of time remaining in the participant recruitment window. 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 priori the sponsor would propose to discontinue the study if either of the conditions below were met (unless there is an indication that recruitment is expected to considerably increase during the remainder of the recruitment period):

- Roctavian Cohort is expected to include ≤33 persons (<50% of the target sample size for the Roctavian Cohort)
- SoC Cohort is expected to include <67 persons (target sample size of the Roctavian Cohort)

A futility assessment will also be included as part of the 36-month and 54-month interim analyses to determine the observed ABR of each cohort. The sample size calculation conducted a priori (see Section 10.1) will be re-calculated based on the observed ABR of each cohort at these timepoints. Implications on study interpretation will be discussed in the reports associated with these interim analyses. Continued conduct of the study as described in the original study protocol based on the futility assessment at these timepoints will be discussed with the G-BA.

Any changes to the conduct of the study and AbD based on the futility assessment will be made in agreement 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 may not be recorded in the data source (ie, AbD).

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. Monitoring of safety data via routine on-site and remote monitoring visits (see Section 11.8) will be utilized to ensure that relevant targeted AEs 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 medicinal products and devices to the relevant competent authority (Model Professional Code for Physicians in Germany - MBO-Ä 1997).

9.2. BioMarin Pharmacovigilance Contact Information

BioMarin Pharmacovigilance contact information is as follows:

BioMarin Pharmaceutical Inc.

Address: 105 Digital Drive
Novato, CA 94949
Phone: +1 (415) 506-6179
Fax: +1 (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, 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, λ_Roctavian= 0.85) and a value for the overdispersion (ϕ = 1.5). This results in a total sample size of at least 397 participants (Roctavian Cohort n = 67, SoC Cohort n = 330) (Zhu 2017).

Based on current estimates of participant enrollment, the study will be powered based on the ABR approach. 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.

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 if data is missing for a variable required for a specific analysis. Minimal missing data is expected as most fields required for the analysis in the DHR are mandatory and data monitoring (see Section 7.1.2) will ensure timely and completeness of data entry for all relevant fields.

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 participants achieving the minimal clinically important differences [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 (eg, 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 recruitment period.
- **SoC Cohort**: PwSHA without a history of or current inhibitors treated with exogenous FVIII replacement therapies or emicizumab and not administered Roctavian during the study recruitment 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. 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 models. Hemostatic treatment variables will similarly be compared.

10.3.2. Approaches to Estimating Comparative Effectiveness

10.3.2.1. Treatment Policy vs. Hypothetical Estimand

Due to the non-randomized, non-interventional nature of this study, two estimands will be considered when estimating the comparative effectiveness of Roctavian to SoC – the treatment policy estimand and the hypothetical estimand. The treatment policy estimand ignores intercurrent events (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.

Due to the study design, along with the management and administration of Roctavian gene therapy, the treatment policy (similar to intent to treat analysis) is likely to be overly conservative in the setting of this study and the hypothetical estimand is expected to provide more clinically interpretable results. In particular, after the administration of Roctavian, PwSHA will continue their SoC prophylaxis therapy in the initial weeks after infusion and

therefore have a period where bleeding events and hemostatic treatment utilization are not reflective of the treatment effect of only Roctavian. Additionally, participants in the Roctavian Cohort may return to prophylaxis, and due to the non-interventional design PwSHA in the SoC Cohort may switch to Roctavian after the study recruitment window. Further, the hypothetical estimand is consistent with the analyses described in the summary of product characteristics (SmPC) (BioMarin Intl. Ltd. 2022) and would allow for consistency of interpretation between this study and data described in the SmPC. Although the study sponsor's position is that the hypothetical estimand will provide more clinically interpretable results, the G-BA resolution dated 21, Sept 2023 (AM-RL 2023b) required the conduct of analyses based on the treatment policy estimand. Therefore, analyses will be conducted and reported utilizing both estimands. Consistency in results for the different estimands and impact on the interpretation of results will be discussed in the interim and final reports.

10.3.2.2. Treatment Policy Estimand

Analyses based on the treatment policy estimand will describe outcomes from index through the end of the follow-up period for both the Roctavian Cohort and SoC Cohort. A participants' time in the analysis will only be censored in the event of a withdrawal, loss to follow-up, death or enrollment in an interventional trial. Follow-up will be censored based the earliest date after index of withdrawal, loss to follow-up, enrollment into an interventional 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). Due to the non-interventional nature of the study and AbD, a participant in the SoC Cohort may subsequently receive Roctavian during follow-up after the recruitment period, if this occurs this participant will be excluded from the analysis. If a participant in the Roctavian Cohort returns to prophylaxis with another hemostatic therapy (eg, exogenous FVIII or emicizumab), this participant will be maintained in the analysis (ie, not excluded from the analysis) as there is a potential continued benefit of the gene therapy after prophylaxis is resumed for effectiveness outcomes and potential long term risk of safety events associated with the gene therapy.

Outcomes for participants in the SoC Cohort who are treated with Roctavian during follow-up after the recruitment period, and are excluded from the analysis, will be described separately. Outcomes will be described for the period these participants were on SoC (index date to date of Roctavian infusion) and treated with Roctavian (date of Roctavian infusion through the end of follow-up).

Figure 2 below illustrates the treatment policy estimand analysis.

Figure 2: Analysis Schema for Treatment Policy Estimand

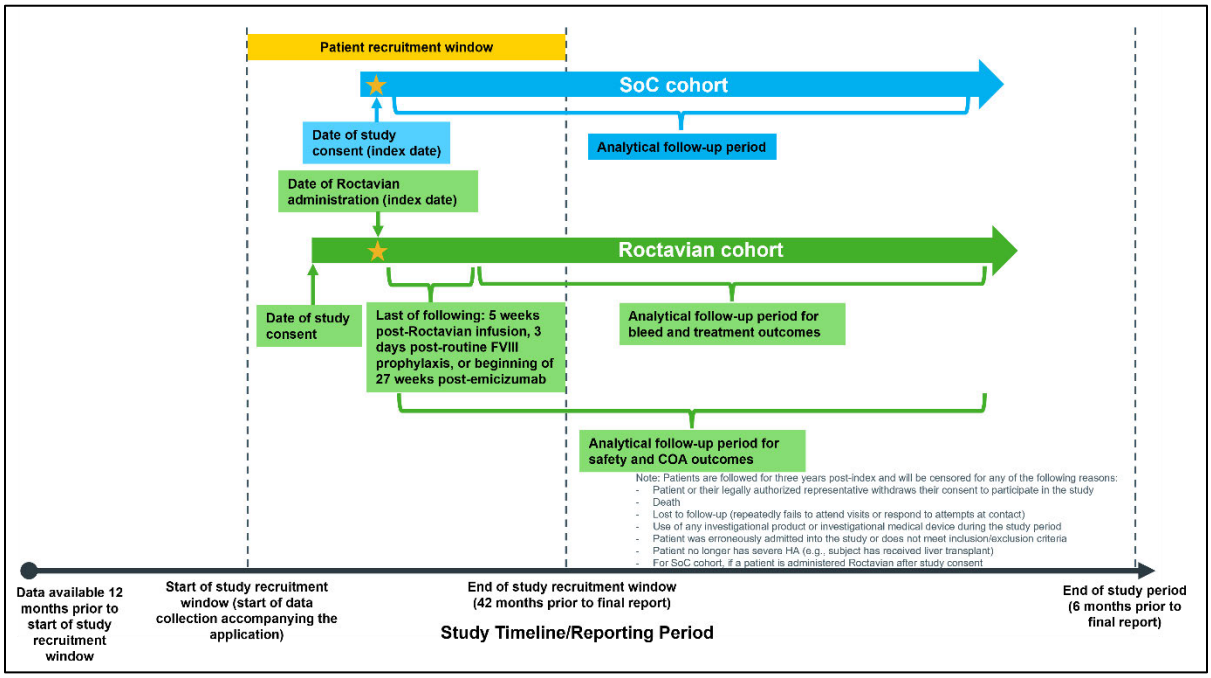


Figure note: Outcomes described from index through the end of the follow-up period for both the Roctavian Cohort and SoC Cohort. A participants' time in the analysis will only be censored in the event of a withdrawal, loss to follow-up, death or enrollment in an interventional trial (based on earliest date of). Any participant in the SoC Cohort who subsequently receives Roctavian during follow-up after the recruitment period will be excluded from the analysis.

10.3.2.3. Hypothetical Estimand

Analyses based on the hypothetical estimand will describe outcomes during the follow-up period for both the Roctavian Cohort and SoC Cohort, minimizing time periods during which outcomes are confounded by exposure to both gene therapy and SoC prophylaxis. As PwSHA administered Roctavian will remain on prophylaxis for a time following the index date as endogenous FVIII production initiates, the analytical follow-up period for outcomes such as bleeding events and hemostatic therapy utilization for the Roctavian Cohort will begin 5 weeks post-infusion or 3 days after the end of routine FVIII prophylaxis (whichever 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. Participants in the Roctavian Cohort will be censored at the time of resumption of SoC prophylaxis and participants in the SoC Cohort who subsequently receive Roctavian during follow-up after the recruitment period, will be censored on the date of Roctavian infusion. As with the treatment policy estimand, for both cohorts a participant's time in the analysis will be censored in the event of a withdrawal, loss to follow-up, death or

enrollment in an interventional trial. Follow-up will be censored based the earliest date after index of any of the censoring events described above.

Figure 3 below illustrates the hypothetical estimand analysis.

Figure 3: Analysis Schema for Hypothetical Estimand

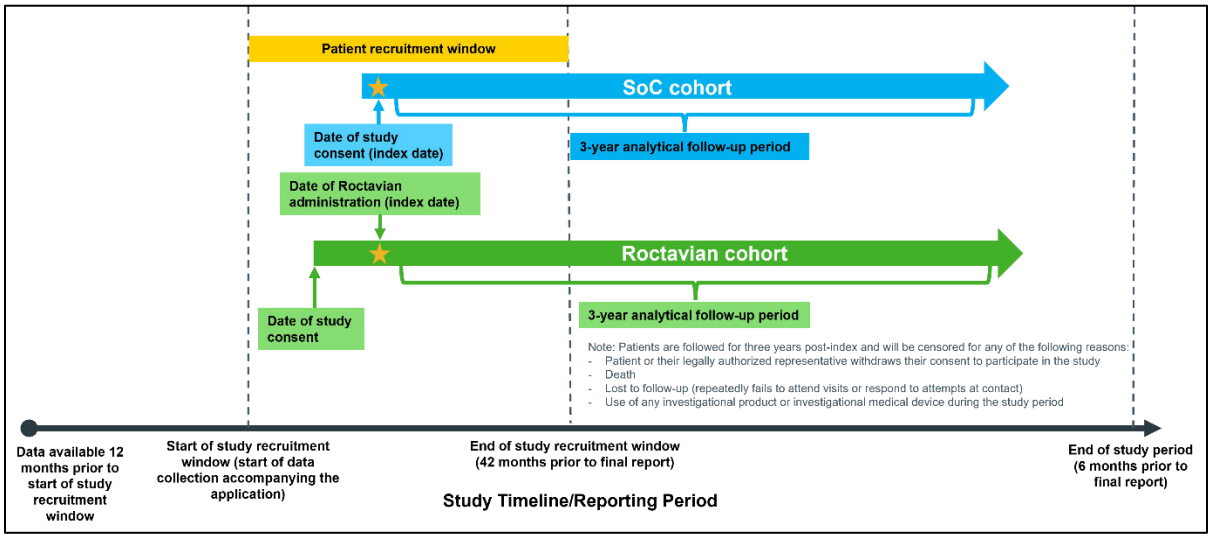


Figure note: For the Roctavian Cohort, analytical follow-up period for outcomes such as bleeding events and hemostatic therapy utilization will begin on 5 weeks post-infusion or 3 days after the end of routine FVIII prophylaxis (whichever occurs later), or 27 weeks after end of emicizumab prophylaxis consistent with analyses of the Roctavian clinical trials. Participants in the Roctavian Cohort will be censored at the time of resumption of SoC prophylaxis. For the SOC Cohort, analytical follow-up period of the SoC Cohort will begin on the index date. Participants in the SoC Cohort who subsequently receive Roctavian during follow-up after the recruitment period, will be censored on the date of Roctavian infusion.

10.3.3. 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 participants to obtain an unbiased estimate of treatment effect.

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

Propensity scores 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 have been identified based upon variables from a literature review of factors associated with bleeding, previous PS development for a comparison of Roctavian to FVIII prophylaxis based on studies that were part of the Roctavian clinical development (Liu 2022; Oldenburg 2024; see Appendices for further details), and clinical input from health care practitioners

(HCPs) in Germany managing PwSHA. Statistical relationships between potential variables and treatment cohort (as defined in the SAP) for the study data, along with clinical input on variables to include regardless of statistical relationship will be utilized to select variables included in the propensity score.

10.3.3.1. Variable identification based on literature, previous work, and clinical HCP input

Prior to the initiation of data collection, a comprehensive literature review was conducted to identify the risk factors or covariates associated with bleeding events among PwSHA. No real world data is currently published on characteristics associated with usage of gene therapy compared to other hemostatic therapies. The findings from this review identified a list of potential variables to be assessed in the PS. The comprehensive literature review was designed to capture the most relevant and high-quality studies based on a fit-for-purpose search strategy developed using key words, MeSH terms, and Boolean operators. There were no date or geographic restrictions for the search, but only articles published in English were included. In addition, meeting abstracts were also excluded. After a comprehensive search strategy was developed (see Appendices for details), the search was executed on November 21, 2023, across the following online databases: Embase, OVID Medline, and the Cochrane Library (CDSR/CENTRAL).

Utilizing the Population, Intervention, Control, Outcome, and Study Design (PICOS) framework, fit-for-purpose study selection criteria was developed (see Appendices). Study selection was conducted in two phases, title/abstract screening, and full-text screening. The initial title and abstract screening was completed by one reviewer (using a conservative approach – including articles that might have missing/unsure PICOS criteria), while subsequent full-text screening was completed by two independent reviewers, where conflicts were resolved between the two reviewers. In addition to the PICOS criteria, only articles that examined the association between HA treatment and bleeding events while considering covariates, either as part of the study design (ie, pre-randomization stratification or matching) or adjustments in the analysis, were included.

A data extraction form was created, and pilot tested including information on study characteristics, patient characteristics/study population, analysis details, and covariates considered in the study design or analysis of included studies. Once the data extraction form was pilot tested, the first reviewer extracted data based on the presented columns, while the second reviewer verified all the extracted data for quality assurance purposes. see Appendices for further details for data extraction fields. After completion of the data extraction, a qualitative synthesis of the included articles was conducted to summarize the articles included in the literature review and to recommend a list of covariates to include in the PS. Overall, the comprehensive literature review included 14 unique studies for covariate assessment. After HCP expert review, one additional study (Chowdary 2022) was also considered to provide recommendations for covariates to include in the PS in order to

compliment the results from the comprehensive literature review. This study used predictive modeling to identify predictors of long-term ABR during prophylaxis with EHL FVIII.

In addition to the comprehensive literature review results, HCP expert advice and previous work on developing PS for the comparison of Roctavian to FVIII prophylaxis (Liu 2022; Oldenburg 2024; see Appendices for further details) has informed/confirmed the list of potential variables to assess for inclusion in the PS. In particular, HCPs in Germany treating PwSHA with either Roctavian or SoC products advised the study team regarding overall study conduct and interpretation, as well as providing input into variables identified for PS inclusion. HCPs provided input into variables both associated with the endpoint of bleeding events as well as factors associated with choosing Roctavian treatment.

Table 9 outlines the potential variables to include in the PS based on the comprehensive literature review, expert physician input, and prior comparative Roctavian versus FVIII prophylaxis studies PS development along with considerations for inclusion based on clinical relevance, potential statistical associations, and anticipated correlations between variables. Prior bleeding history, ABR (12 months prior to index date), will be included in the PS regardless of statistical significance due to clinical significance based on feedback from German physicians. See the SAP for further information regarding operationalization of the variables for PS assessment in the SAP.

Table 9: List of potential variables for inclusion in PS

Variable	Literature review	From previous PS work	Clinical expert opinion	Considerations
Baseline/prior bleeding history (eg, ABR)	✓	✓	✓	Include regardless of statistical association, based on clinical relevance
Baseline FVIII utilization	✓	✓	✓	Include based on statistical association and correlation with other variables (eg, baseline/prior bleeding history and baseline prophylaxis class)
Baseline prophylaxis class (FVIII vs. emicizumab)	✓	✓	✓	Include based on statistical association and correlation with other variables (eg, baseline/prior bleeding history and FVIII utilization)
Age	✓	✓	✓	Include based on statistical association
Height, Weight and/or BMI	✓	✓	✓	Include based on statistical association
Baseline von Willebrand factor (IU/mL)	✓	X	✓	Include based on statistical association
Number of target joints	✓	✓	X	To be considered depending on statistical association and correlation with other variables (eg, baseline/prior bleeding history and joint health score)
Joint health (eg, baseline/prior HJHS)	X	X	✓	To be considered depending on statistical association and correlation with other variables (eg, baseline/prior bleeding history and number of target joints)
Baseline/prior type of bleeds	X	X	✓	To be considered depending on statistical association and correlation with other variables (eg, baseline/prior bleeding history and target joints)
Geography (HTC/site/region/country)	✓	✓	X	Site to be considered depending on statistical association and correlation with other variables
Prophylaxis class switching (eg, SHL/PD to EHL/emicizumab)	✓	✓	X	To be considered depending on statistical association and correlation with other variables

Variable	Literature review	From previous PS work	Clinical expert opinion	Considerations
Baseline/prior pain (eg, BPI-sf)	X	X	✓	To be considered depending on statistical association and correlation with other variables (eg, target joints and HJHS)
Baseline/prior QoL (eg, Haemo-QoL-A)	X	X	✓	To be considered depending on statistical association and correlation with other variables
Activity status	X	X	✓	Not considered as this there is no validated questionnaire for lifestyle factors in PwSHA
Baseline/prior history of liver fibrosis/cirrhosis	✓	X	X	Significant liver fibrosis/cirrhosis is accounted for by the exclusion criteria, but less severe liver fibrosis to be considered based on statistical association
Baseline/prior history of hepatitis B and C	✓	X	X	Not considered as this is accounted for by study exclusion criteria
Baseline/prior history of HIV positivity	✓	X	X	Include based on statistical association
Baseline/prior history of cancer	✓	X	X	Include based on statistical association
Baseline/prior history of hypertension	✓	X	X	Include based on statistical association
Baseline/prior history of osteoporosis	✓	X	X	Include based on statistical association
Adherence to treatment	✓	X	X	Not considered as there is not enough prior literature/evidence to suggest as factor related to bleeding outcomes; confirmed by clinical expert
Genotype	X	X	X	Not considered as this is a factor for inhibitor development but not bleeding outcomes and accounted for by study exclusion criteria for history of or current inhibitors

ABR, Annualized bleeding rate; BMI, body mass index; EHL, extended half-life; FVIII, coagulation factor VIII; HIV, human immunodeficiency virus; HTC, hemophilia treatment center; PD, plasma-derived; PwSHA, people with severe hemophilia A; QoL, quality of life; SHL, standard half-life.

Note: Other variables identified in the literature review but not outlined in Table 9, due to lack of relevance to this study and the association comparing Roctavian and SoC and bleeding outcomes, were ethnicity, treatment duration, pharmacokinetic (PK)-guided dosing use, prophylaxis vs on-demand treatment, concurrent medications (bypass agents, non-steroid anti-inflammatory drugs, tranexamic acid, and corticosteroid), and hemophilia severity.

10.3.4. Exploration of unmeasured confounding

As it may not be feasible to collect all potential variables associated with treatment choice or bleeding outcomes (such as individual lifestyle choices) due to the nature of the study and maximizing data quality for the study when working with an existing registry (see Section 10.5), it is possible that residual confounding exists as a result of unobserved variables not included in the PS, which could influence the direction and/or magnitude of results observed. Therefore, the E-value, as reported by VanderWeele and Ding, will be used to explore this further (VanderWeele 2017).

The E-value is the minimum strength of association, on the risk ratio scale, that an unmeasured confounder would need to have with both the treatment and outcome, conditional on the measured covariates, to explain away a treatment–outcome association. The E-value focuses on the magnitude of the confounder associations that could produce confounding bias equal to the observed treatment–outcome association.

E-value calculations are straightforward. For an observed risk ratio of RR:

$$\text{E-value} = RR + \text{sqrt}\{RR \times (RR - 1)\}$$

The formula applies to a risk ratio greater than 1; for a risk ratio less than 1, one first takes the inverse of the observed risk ratio and then applies the formula.

The interpretation of the E-value along with a qualitative assessment, including clinical input from HCPs in Germany, will be incorporated into the interpretation of results.

10.3.4.1. Baseline comparison of groups for propensity score development

Participant 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.

10.3.5. Application of the Propensity Score

Multiple PS adjustment methodologies have been 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 based on the hierarchy of methods outlined in the SAP. 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 inverse probability of treatment weighting (IPTW). IPTW will utilize all available data compared to matching approaches and estimate the Average Treatment Effect (ATE). Sensitivity analyses will be performed using alternative methods. Propensity score matching (PSM) is planned to be utilized as the main sensitivity method *a priori*. As the primary analysis plans to utilize IPTW and the *a priori* sensitivity analysis is planned to be PSM, these methods have been discussed below in Section 10.3.5.1.

Inverse probability treatment weighting IPTW will be implemented to create a baseline reference of propensity score weights for comparison. Using this approach, each participant is assigned a weight representing the inverse probability of being assigned to their respective group. Thus, IPTW aims at giving more importance (ie, more "weight") to those participants that have unexpected propensity score values. For the treated group (Roctavian Cohort), the weight, W, assigned in the IPTW method for each individual, i, based on propensity score, P_i, is:

$$W_i = \frac{1}{P_i}$$

For the control group (SoC Cohort), participants receive weights of:

$$W_i = \frac{1}{(1 - P_i)}$$

As the characteristics of the population that will be treated with Roctavian are unknown at the time of this protocol being drafted, it is possible that large differences in characteristics between the Roctavian and SoC Cohort will exist. If this is the case, some participants may have extreme PS weights and, though representing a small portion of the observed population, have a disproportionate influence on the analysis. This outsized influence of individuals with extreme weights may increase variance and confidence intervals of the average treatment effect estimate (Chesnaye 2022). The SAP outlines approaches that will be taken in the case of extreme weights (eg, trimming) and criteria when these approaches will be implemented.

10.3.5.1. Propensity score matching

Propensity score matching will be considered *a priori* for a sensitivity analysis and initially be performed using the procedure of 1:4 matching. The PSM method matches each participant in the Roctavian Cohort with four participants in the SoC Cohort exhibiting the nearest PS (this is also known colloquially as 'greedy' matching) without replacement. 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. If the 1:4 matching ratio is not achievable at the specified caliper with >90% of the Roctavian Cohort matched to four SoC participants, a 1:3 matching ratio will be attempted, followed by a 1:2 matching ratio and then a 1:1 matching ratio as needed based on the requirement to match >90% to the relevant ratio. If the 1:1 matching ratio is not achievable, results for PSM will not be reported.

10.3.6. Primary Objective

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

Annual bleeding rates for treated bleeding events (see Table 6) will be compared between the Roctavian Cohort and SoC Cohort after PS adjustment. *A priori* the PS adjustment is planned to be implemented via IPTW. 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 participant 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 reduced for final analyses due to censoring (see below).

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 Cohort and SoC Cohort utilizing a two-sample t-test (two-sided).

10.3.7. Secondary Objectives

10.3.7.1. 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 Cohort and SoC Cohort after PS adjustment. The analysis approach will be consistent with the primary objective (see Section 10.3.6) regarding PS adjustment approach, analysis of the full follow-up time along with annual increments, as well as measurement of treatment effect.

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

Proportion of participants with zero bleeding events for all bleeding outcomes described in Table 6 will be compared between the Roctavian Cohort and SoC Cohort after PS adjustment, generally consistent with the analysis approach for ABRs (see Section 10.3.6 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 participants with zero bleeding will only include those participants with follow-up for the full time over which the proportion is calculated. Additionally, the measurement of treatment effect for these analyses will be the relative risk and 95% confidence interval between participants in the Roctavian Cohort and SoC Cohort having zero bleeding events.

10.3.7.3. Objective: To compare the use of hemostatic medications.

The use of hemostatic medications will be compared between the Roctavian Cohort and SoC Cohort after PS adjustment, generally consistent with the analysis approach for ABRs (see Section 10.3.6 above) regarding PS adjustment approach, and analysis of the full follow-up time along with annual increments. Comparisons will be made regarding the variables in Table 7.

The proportion of participants 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 relative risk of participants utilizing any hemostatic treatments specifically for bleeds or short-term prophylaxis will be compared consistent with the proportion of participants with zero bleeding events. Also consistent with the analysis of the proportion of participants 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 administered 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 Cohort and SoC Cohort utilizing a two-sample t-test (two-sided). Similar to the analyses of the proportion of participants 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 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 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 Cohort and SoC Cohort utilizing a two-sample t-test (two-sided).

10.3.7.4. 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 utilized to describe the overall trend in the HJHS over time. The mean change from baseline to final assessment approximately 3 years after index date will be compared between the Roctavian Cohort and SoC Cohort.

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. Participants 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.

10.3.7.5. Objective: To compare safety events of interest.

Safety events outlined in Table 8 will be described in each cohort. Summaries of the proportion, event rate, and incidence rate of each of the safety events among all participants by cohort will be provided. Safety events will be described from index through follow-up. All participants will be included in analyses of event and incidence rates, while analyses of the proportion of participants will only include those participants with follow-up for the full time over which the proportion is calculated. Safety outcomes will be compared as relative risks based on the incidence of an event for analyses of the treatment policy estimand and as incidence rate ratios censoring a participants person time at the time of the event for analyses of the hypothetical estimand.

10.3.7.6. Objective: To describe time to resumption of prophylactic treatment among participants administered Roctavian

Time between Roctavian administration (index date) and resumption of hemostatic prophylaxis (defined 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. Treatment utilization patterns in the 3 and 6 months after the resumption of prophylaxis will be described regarding the number of infusions/injections by prophylaxis treatment class, total FVIII dose for participants returning to prophylaxis with FVIII, and frequency of infusions/injections will be described.

10.3.8. 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 (eg, SHL FVIII, EHL FVIII, PD FVIII, and emicizumab), age groups, 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 for subgroups will be described during the 18-month interim report, though analyses are planned *a priori*. 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 characteristics of the sub-cohort, which will impact the ability of the PS to address confounding, as well as sample size. 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 characteristics and sample size). Feasibility of analyses will also consider the ability to conduct comparisons for all vs specific objectives (eg, it may be possible to conduct sub-group analyses for the primary objective, but not for secondary objectives due to missing data). It is assumed a priori that analyses will be feasible.

In addition to the evaluation of the pre-specified sub-group analysis regarding SoC therapeutic classes and AAV 5 antibody status, other sub-group 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 will be detailed in the SAP and discussed in the interim reports (described below).

10.4. Interim Analyses

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

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. Study sites will be asked to update data for all AbD participants approximately 6 months prior to the planned interim analysis and will be supported by site monitors through on-site monitoring and routine monitoring visits to ensure that all available data for enrolled participants are recorded into the DHR prior to the planned interim analysis. 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 10.3.8. The feasibility of sensitivity analyses, along with other sub-group 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 Germany, 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 participants managed at the same site will be able to be identified. If it is ultimately not possible to identify participants at the same site, the analysis will be limited in controlling for differential clinical management practices (eg, 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 10.3.8, the characteristics of the population that utilizes Roctavian in the real world is not currently known 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) 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 the 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 until 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 (eg, participation in sports and physical

activities) and personal experience with hemophilia A (eg, 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 participant 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-participant 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. In addition to variables that are not feasible to capture in an observational registry, the non-interventional nature of the study reflecting a range of real-world practice in German could introduce confounding that cannot be fully addressed with PS or specific applications of the PS (eg, matching). For example, persons with severe hemophilia A are recommended to be treated with hemostatic prophylaxis, though a small portion of the severe hemophilia A population in Germany may still be utilizing an on-demand treatment regimen. Persons utilizing an on-demand regimen are likely to have a higher baseline bleeding rate, as prophylaxis is associated with reduce bleeding events. All persons administered commercially available Roctavian are expected to have received hemostatic prophylaxis treatment for at least 12 months by the time that a participant will be treated with Roctavian gene therapy. If persons treated with an on-demand regimen for part of the baseline period enroll into the SOC Cohort, these participants may have outlier propensity scores which may not be able to be matched. The proportion of on-demand participants in the SOC Cohort, as well as impact of these participants on the analysis will be discussed in interim and final reports.

For safety outcomes, PS may be less likely to control for potential confounding due to the expected rarity of the safety events of interests. The risk of spurious findings for the safety comparisons are particularly notable for 'all-cause' outcomes that do not consider relationship to hemophilia treatment as characteristics of the cohort. For example, if one cohort is older, events due to unrelated causes (ie, risks associated with older age) could be misinterpreted to be associated with a product.

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/REB approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.

The investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB/IEC/REB annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC/REB
- Notifying the IRB/IEC/REB of Serious Adverse Events (SAEs) or other significant safety findings as required by IRB/IEC/REB 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 participant or his legally authorized representative and answer all questions regarding the study.

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

Participants must be informed that their participation is voluntary. Participants 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 participant consents and the IRB/IEC/REB 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 participant to the participant'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.

Participants must be re-consented to the most current version of the ICF(s) during their participation in the study. Participants 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 participant or the participant'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 participant data collection and data entry into the DHR.

Validation of participant 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 participant identifiers) for at least 15 years after the completion or discontinuation of the study. Participant 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 participant data, including the use of participant numbers in the DHR. A list linking participant identification numbers with participant names and other personal information will be kept in a secure place, separate from the participants' medical records. BioMarin will follow all applicable regulations and guidelines in the relevant locality, country, and/or region to protect the privacy of participant data.

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

The participant 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 participant, who will be required to give consent for their data to be used as described in the informed consent.

The participant 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/REB 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

Selected sites will be managed and monitored throughout the duration of the study according to the approved Clinical Operations Plan (ie, 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 and on-site visits.

Prior to commencing activities, an on-site, site initiation visit will be performed at each study site selected to participate and will be performed by monitors trained to conduct site initiation visits. Training of the monitors will be performed by the sponsor or designee.

During the initiation visit, monitors will train physicians and appointed site personnel involved in this study, on the protocol, procedures and the creation and maintenance of accurate source records.

On-site monitoring visits will involve 100% source data verification on all data fields relating to inclusion and exclusion criteria and primary endpoint data fields against entries made into the DHR. A further 10% of randomly selected participants will have all remaining endpoints source data verified against entries made into the DHR.

All source data should be captured in source medical records that are standard practice for the site. Examples of source documents that may be used in this study may include: Participant medical notes and/or records; Site specific source document worksheets, if used; Laboratory reports and other test results; Informed Consent Forms; Hospital records for associated SAEs; Patient Reported Outcomes questionnaires.

Source data verification will aid in the reduction of missing, or incomplete data in the DHR, however due to the non-interventional nature of this routine data collection, complete avoidance of missing or implausible data is impossible.

To ensure timely completeness of data into the DHR, on-site and remote site visits will be performed, and it is anticipated that at least 2 routine on-site monitoring visits, per annum, per site will be conducted. The first on-site monitoring visit will be performed within 4 weeks of inclusion of the first participant at each study site.

Remote site visits may occur in addition to, or in place of on-site monitoring visits, if restrictions due to COVID-19 pandemic or any other unforeseen events prevent on-site visits occurring. In between on-site monitoring visits, regular contact with site staff personnel will be maintained to provide support, re-training (as needed) and to provide reminders on data completion and data entry.

Further details will be outlined in the Clinical Operations Plan.

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/.

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14. APPENDICES

Appendix 1 - Protocol Amendment History

None

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

Appendix 3 – Literature Review Methods and Results

270-603

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: April 26, 2024, Updated

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 in Charge**

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 (observational data collection)
ABR	Annualized bleeding rate
ADR	Adverse drug reaction
AE	Adverse event
AIC	Akaike information criterion
AIR	Annualized infusion/injection rate
ATE	Average treatment effect
ATT	Average treatment effect on the treated
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
DXA	Dual-energy X-ray absorptiometry
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
HCP	Healthcare practitioner
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
MeSH	Medical Subject Headings

mg	Milligram
ml	Milliliter
mm HG	Millimeters of mercury
OR	Odds ratio
PD	Plasma-derived
PICOS	Population, Intervention, Control, Outcome, and Study Design
PJ	Problem joints
PK	Pharmacokinetic
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
SmPC	Summary of product characteristics
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 compare 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 people with severe hemophilia A (PwSHA).
The study objectives and endpoints below will compare Roctavian and SoC prophylaxis treatments with exogenous coagulation factor VIII (FVIII) or emicizumab, unless otherwise noted.
<table>
<tr><th>Objectives</th><th>Endpoints</th></tr>
<tr><td>Primary:</td><td></td></tr>
<tr><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>Secondary:</td><td></td></tr>
<tr><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>• To compare the proportion of people 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>• To compare the use of hemostatic medications.</td><td>• Prophylactic hemostatic treatments.
• On-demand hemostatic treatments.</td></tr>
<tr><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>• 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, malignant neoplasms, and severe liver disease (liver failure or cirrhosis).</td></tr>
<tr><td>• To describe time to resumption of prophylactic treatment among persons administered Roctavian.</td><td>• Resumption of prophylactic hemostatic treatments.</td></tr>
</table>
</td></tr>
</table>

Study Duration	Start of data collection accompanying the application to approximately 6 months prior to the date of the final report required by the G-BA resolution for AbD.
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 Cohort.
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 (i.e., Deutsches Hämophilieregister [DHR]) database previously administered Roctavian or hemostatic prophylaxis with exogenous FVIII or emicizumab during the study recruitment period with no history of (or current) FVIII inhibitors, no acute infections (such as acute respiratory infections or acute hepatitis) or uncontrolled chronic infections (such as chronic active hepatitis B), and/or no known significant hepatic fibrosis or cirrhosis.

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

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

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 supplementation 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 undertaken to fulfil the Federal Joint Committee (G-BA; Gemeinsamer Bundesausschuss) requirement for Routine Data Collection and Evaluations (as described in Section 4.2 of the corresponding Study Protocol). Specifically, this study will provide data on the comparative effectiveness of Roctavian to standard of care (SoC) hemostatic prophylaxis treatments (see Section 4.2.2 of the Study Protocol) among people with severe HA (PwSHA) without a history of (or current) 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 exogenous 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 people 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, malignant neoplasms, and severe liver disease (liver failure or cirrhosis)
• To describe time to resumption of prophylactic treatment among persons 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 exogenous FVIII replacement therapies or emicizumab in Germany. Study participants will be followed based on data prospectively entered into the German Hemophilia Register (i.e., Deutsches Hämophilieregister [DHR]). All participants are expected to have previously enrolled in the DHR per 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 recruitment period beginning approximately 3 months after this protocol is agreed with the G-BA (to allow for ethics committee approval of the final protocol) and ending approximately 42 months prior to the date of the final report required by the G-BA resolution for the AbD. This study recruitment period 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.

Participants will be assigned to a study cohort based on the treatment that was received during the recruitment period. On and/or before the start of the study recruitment period, participants would have received SoC treatments, thus this study is centered around a prevalent new user design.[10] All participants receiving Roctavian during the recruitment period will be assigned to the Roctavian Cohort. Participants receiving SoC hemostatic prophylaxis treatment only during the recruitment period 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 consents to the AbD while on SoC and subsequently receives Roctavian during the recruitment period, inclusion/exclusion criteria will be reassessed at the time of Roctavian administration. For these participants, baseline assessments, including patient reported outcome measures, will also be re-assessed at the time of Roctavian administration. If a participant in the SoC Cohort subsequently receives Roctavian during follow-up after the recruitment period, their data will be censored for analysis. Study participants will be followed consistent with the Study Elements of Interest (see Study Protocol and Section 7.4) from index through the follow-up period. 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 be completed approximately 6 months prior to the final report required to be submitted to the G-BA. Figure 1 illustrates the overall study conduct. The study completion date is based on allowing time to analyze data and submit a final report on the AbD defined by the G-BA resolution. Changes to the AbD defined deadlines for the final report would result in changes to the study completion timeframe, as well as the recruitment window described above.

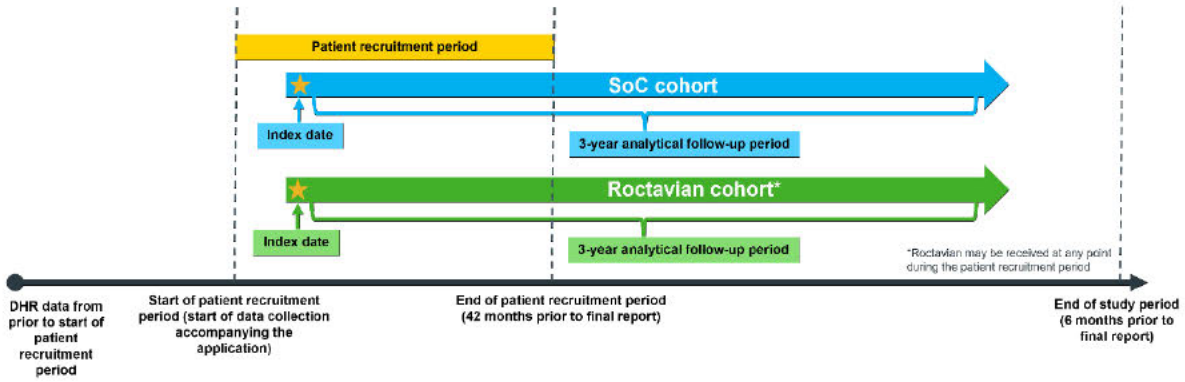

Figure 1: Study Schema

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 (all cause death, hemophilia-related death, adverse events (AEs) leading to hospitalization and death, and targeted AEs of FVIII inhibitor development, thrombotic events, new malignancies, and severe liver disease). PwSHA in Germany are generally seen at a hemophilia treatment center (HTC) every 6 months and therefore it is expected that clinical outcome assessments of quality of life and pain would be assessed at those timepoints, with joint health assessed at least annually.

Comparisons of safety will also be conducted. 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. Potential variables to be included in the propensity score, based on association with the primary outcome, were identified from the literature and discussion with German clinicians. Exact variables included in the propensity score will be based on statistical, as well as clinical associations, between baseline characteristics and the likelihood of receiving Roctavian therapy.

7.2. Study Estimand

7.2.1. Treatment Policy vs. Hypothetical Estimands

Due to the non-randomized, non-interventional nature of this study, two estimands will be considered when estimating the comparative effectiveness of Roctavian to SoC - the treatment policy estimand and the hypothetical estimand. The treatment policy estimand ignores intercurrent events (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.

Due to the study design, along with the management and administration of Roctavian therapy, the treatment policy (similar to intent to treat analysis) is likely be overly conservative in the setting of this study and the hypothetical estimand is expected to provide more clinically interpretable results. In particular, after the administration of Roctavian, PwSHA will continue their SoC prophylaxis therapy in the initial weeks after infusion and therefore have a period where bleeding events and hemostatic treatment utilization are not reflective of the treatment effect of only Roctavian. Additionally, participants in the Roctavian Cohort may return to prophylaxis, and due to the non-interventional

design PwSHA in the SoC Cohort may switch to Roctavian after the study recruitment window. Further, the hypothetical estimand is consistent with the analyses described in the summary of product characteristics (SmPC)[11] and would allow for consistency of interpretation between this study and data described in the SmPC. Although the study sponsor's position is that the hypothetical estimand will provide more clinically interpretable results, the G-BA resolution dated 21, Sept 2023[12] required the conduct of analyses based on the treatment policy estimand. Therefore, analyses will be conducted and reported utilizing both estimands. Consistency in results for the different estimands and impact on the interpretation of results will be discussed in the interim and final reports.

7.2.2. Treatment Policy Estimand

Analyses based on the treatment policy estimand will describe outcomes from index through the end of the follow-up period for both the Roctavian Cohort and SoC Cohort. A participants' time in the analysis will only be censored in the event of a withdrawal, loss to follow-up, death or enrollment in an interventional trial. Follow-up will be censored based the earliest date after index of withdrawal, loss to follow-up, enrollment into an interventional 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 +3 years). Due to the non-interventional nature of the study and AbD, a participant in the SoC Cohort may subsequently receive Roctavian during follow-up after the recruitment period, if this occurs this participant will be excluded from the analysis. If a participant in the Roctavian Cohort returns to prophylaxis with another hemostatic therapy (e.g., exogenous FVIII or emicizumab), this participant will be maintained in the analysis (i.e., not excluded from the analysis) as there is a potential continued benefit of the gene therapy after prophylaxis is resumed for effectiveness outcomes and potential long term risk of safety events associated with Roctavian therapy.

Outcomes for participants in the SoC Cohort who are treated with Roctavian during follow-up after the recruitment period, and are excluded from the analysis, will be described separately. Outcomes will be described for the period these participants were on SoC (index to date to Roctavian infusion) and treated with Roctavian (date of Roctavian infusion through the end of follow-up).

Figure 2 below illustrates the treatment policy estimand analysis.

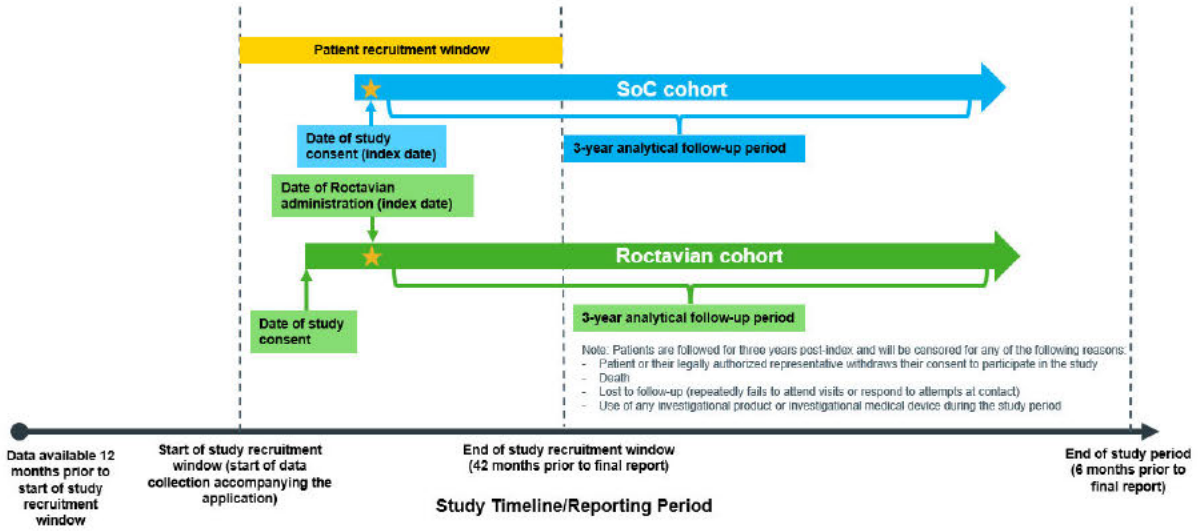

Figure 2: Treatment Policy Estimand Study Schema

Figure note: Outcomes described from index through the end of the follow-up period for both the Roctavian Cohort and SoC Cohort. A participants' time in the analysis will only be censored in the event of a withdrawal, loss to follow-up, death or enrollment in an interventional trial (based on earliest date of). Any participant in the SoC Cohort who subsequently receives Roctavian during follow-up after the recruitment period will be excluded from the analysis.

7.2.3. Hypothetical Estimand

Analyses based on the hypothetical estimand will describe outcomes during the follow-up period for both the Roctavian Cohort and SoC Cohort, minimizing time periods during which outcomes are confounded by exposure to both Roctavian gene therapy and SoC prophylaxis. As PwSHA administered Roctavian will remain on prophylaxis for a time following the index date as endogenous FVIII production initiates, the analytical follow-up period for outcomes such as bleeding events and hemostatic therapy utilization for the Roctavian Cohort will begin on 5 weeks post-infusion or 3 days after the end of routine FVIII prophylaxis (whichever occurs later), or 27 weeks after end of emicizumab prophylaxis consistent with analyses of the Roctavian clinical trials.[13] The analytical follow-up period of the SoC Cohort will begin on the index date. Participants in the Roctavian Cohort will be censored at the time of resumption of SoC prophylaxis and participants in the SoC Cohort who subsequently receive Roctavian during follow-up after the recruitment period, will be censored on the date of Roctavian infusion. As with the treatment policy estimand, for both Cohorts a participants' time in the analysis will be censored in the event of a withdrawal, loss to follow-up, death or enrollment in an interventional trial. Follow-up will be censored based on the earliest date after index of any of the censoring events described above. Figure 3 below illustrates the hypothetical estimand analysis.

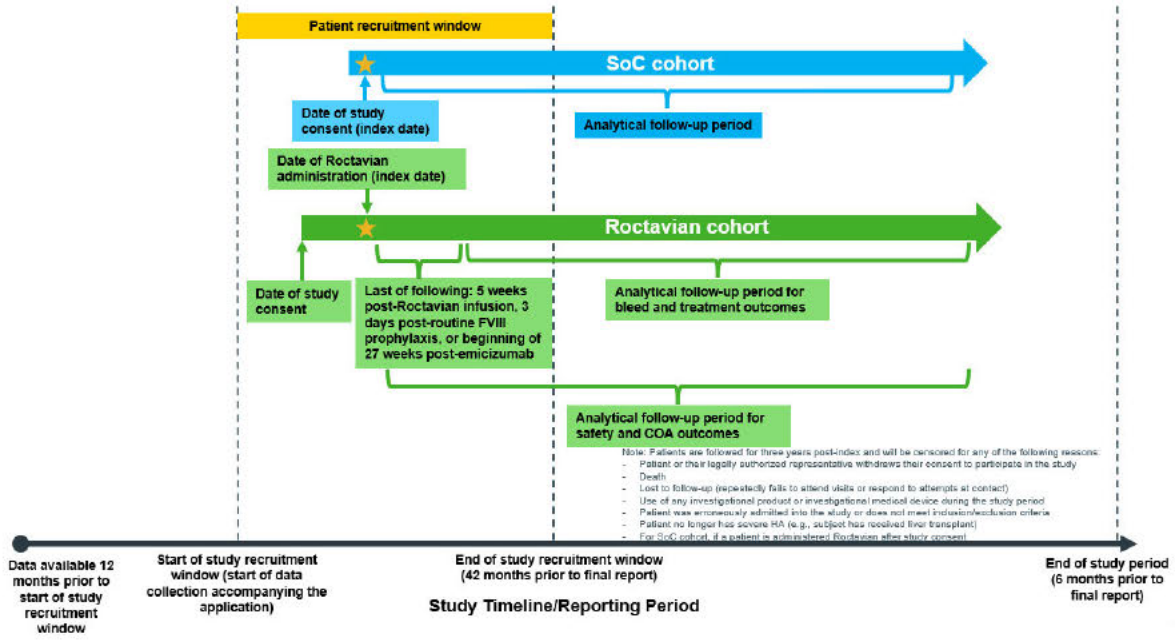

Figure 3: Hypothetical Estimand Study Schema

Figure note: For the Roctavian Cohort, analytical follow-up period for outcomes such as bleeding events and hemostatic therapy utilization will begin on 5 weeks post-infusion or 3 days after the end of routine FVIII prophylaxis (whichever occurs later), or 27 weeks after end of emicizumab prophylaxis consistent with analyses of the Roctavian clinical trials. Participants in the Roctavian Cohort will be censored at the time of resumption of SoC prophylaxis. For the SoC Cohort, analytical follow-up period of the SoC Cohort will begin on the index date. Participants in the SoC Cohort who subsequently receive Roctavian during follow-up after the recruitment period, will be censored on the date of Roctavian infusion.

7.3. Setting

7.3.1. Study Time Period

The study period from the start of data collection accompanying the application to approximately 6 months prior to the date of the final report required by the G-BA resolution for AbD represents the entirety of the dataset. Participants will provide consent during a study recruitment period as outlined in Section 7.1. The 12 months immediately prior to their index date will be utilized for baseline description of clinical variables such as bleeding events and hemostatic medication utilization. It is anticipated that participants will have 12 months baseline data in the DHR prior to the index date, though this is not mandatory. Participants will be followed in the Cohorts for a maximum of 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 deadline. Changes to the AbD defined deadlines for the report would result in changes to the study completion timeframe, as well as the recruitment window described above.

7.3.2. Index Date

For participants in the Roctavian Cohort, the index date will be the date of Roctavian administration during the recruitment period. For participants in the SoC Cohort, the index date will be the date of participant consent into the study during the same recruitment period.

7.3.3. Follow-up Period and Censoring

Participants will be followed for three years post-index date.

7.3.3.1. Censoring Criteria due to Withdrawal and/or Death

Participants will be censored from the study due to any of the following reasons:

- Participant 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
- Participant was erroneously admitted into the study or does not meet inclusion/exclusion criteria
- Participant no longer has severe HA (e.g., subject has received liver transplant)
- For SoC Cohort, if a participant 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 and/or initiate participation in a clinical trial, 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 participants are censored from the study while the recruitment window is ongoing, new participants may be selected for replacement.

7.3.3.2. Censoring and Follow-up Criteria due to Hypothetical Estimand

Analytical Considerations

For the analysis under the hypothetical estimand, the following additional censoring criteria will be applied:

- Treatment switching from SoC to Roctavian (or vice versa) anytime during the study period
- Analytical follow-up time after Roctavian administration before 5 weeks post-infusion or 3 days before the end of routine FVIII prophylaxis (whichever occurs later), or 27 weeks before end of emicizumab prophylaxis (for outcomes such as bleeding events and hemostatic therapy utilization)

7.3.4. Study Population

The study population will include male PwSHA without a history of (or current) inhibitors to FVIII in Germany. Participants 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. Participants will be captured in either the Roctavian or SoC Cohorts based on the treatment they receive during the study recruitment window. 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 enrollment into this study will not inform the treatment strategy.

Participants will be selected into one of two mutually exclusive Cohorts based on the treatment they receive for HA. The Roctavian Cohort will include participants who received Roctavian during the recruitment period. The index date for these participants will be the date Roctavian is administered. The SoC Cohort will include participants who received prophylactic treatment with any of the following SoC treatments, recombinant or human plasma-derived (PD) blood coagulation FVIII or emicizumab. Participants in the SoC Cohort cannot have a history of exposure to Roctavian. Eligibility criteria will be confirmed at time of enrollment based on DHR field that the participant fulfills the AbD inclusion/exclusion criteria.

7.3.5. Participant Selection

7.3.5.1. Inclusion Criteria

Individuals will be included in the study if they meet all the following criteria on the index date:

- Male PwSHA, as recorded in the DHR
- ≥18 years of age at index
- Treatment with Roctavian or SoC hemostatic prophylaxis during the recruitment window
    - Participant administered commercially available Roctavian. Note: Assignment of a therapeutic strategy is not determined by this protocol.
        - OR
    - Has received prophylactic treatment with exogenous FVIII or emicizumab.
- 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

Individuals will be excluded from the study if they meet any of the following criteria on the index date:

- 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
- Presence of acute infections (such as acute respiratory infections or acute hepatitis) or uncontrolled chronic infections (such as chronic active hepatitis B), and/or known significant hepatic fibrosis or cirrhosis at index

7.3.5.3. Inclusion/Exclusion Criteria Variables

Table 2 outlines the variables and operational definitions of the inclusion/exclusion criteria.

Table 2: Inclusion/Exclusion Criteria Variables

Variable	Captured in DHR	DHR data field name	Operational definition/description
Clinical trial participation	Yes	• Participation in clinical trial • Current participation in clinical trial • Name of the clinical trial	• In the last 12 months before index • No (exclude participant 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 • Exclusion criteria confirmed at time of enrollment based on DHR field confirming that the participant fulfills the AbD inclusion/exclusion criteria
History of Inhibitors (ever)	Yes	• Diagnosis • Inhibitor tests against FVIII/FIX positive in this reporting period • Occasion • Positive/ negative result	• Yes/No • Based on any recording of the DHR variables for inhibitors developed before the participant started treatment at

Variable	Captured in DHR	DHR data field name	Operational definition/description
			the current treatment center, positive inhibitor tests after enrollment in the DHR, or use of immune tolerance 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 • Use of ITT will be identified if occasion = "ITT" • Exclusion criteria additionally confirmed at time of enrollment based on DHR field confirming that the participant fulfills the AbD inclusion/exclusion criteria.
Severe HA	Yes	• Diagnosis • Hemophilia severity	• Severe (exclude participant if moderate, mild, or subclinical) • Inclusion criteria additionally confirmed at time of enrollment based on DHR field confirming that the participant fulfills the AbD inclusion/exclusion criteria
Sex	Yes	• Gender	• Male (exclude participant if female or diverse) • Inclusion criteria additionally confirmed at time of enrollment

Variable	Captured in DHR	DHR data field name	Operational definition/description
			based on DHR field confirming that the participant fulfills the AbD inclusion/exclusion criteria
Age	Yes (calculated)	• Year of birth[1]	• Age at Index Date ≥18 years • Confirmed at time of enrollment based on DHR field confirming that the participant fulfills the AbD inclusion/exclusion criteria
Treatment with prophylaxis inclusion	Yes	• Preparation/ medicinal product • Gene therapy	• Participants who are administered Roctavian or SoC medication as recorded in the DHR • For Roctavian Cohort, gene therapy drug = "Roctavian" • For SoC Cohort, participant has received any prophylactic treatment with exogenous FVIII or emicizumab • 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 • Confirmed at time of enrollment based on DHR field confirming that the participant fulfills the AbD inclusion/exclusion criteria

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: Data fields in the DHR are either mandatory to be entered into the registry per DHR practices or will be monitored to ensure completeness of data for analyses, however responses may still be unknown.

1. Date of birth (month/year) is collected in DHR, but only year is available for analysis per DHR practices. An assumed day and month of birth (01 July) for all participants will be implemented to describe approximate age of participants at index.

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.). All variables planned to be utilized for the analysis *a priori* are defined in sections below. If any changes to these *a priori* definitions occur during the study conduct (for example due to changes to the DHR), these additional variables or definitions will be recorded and described in the interim and final reports. For the purposes of this study, DHR data fields referring to "gene therapy" are referring to Roctavian use.

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. Measures will be assessed at the most recent time point prior to the index date, unless otherwise specified.

Table 3: Baseline Variables

Variable	Captured in DHR	DHR data field name(s)	Operational definition/description
Unique participant ID	Yes (Derived)	Unique identifier for participants at an HTC are utilized in the DHR. Outputs from the DHR are anonymized, though a consistent study center code and de-identified participant id at that site will be available to identify participants	• Calculated field based on a de-identified study center code and unique participant code (e.g., participant at study center A may be identified as A-101)
Index date	Yes	• Patient takes part in data collection during the application? • Start of the AbD (date of consent)	• ddmmyyyy • Date of Roctavian administration for Roctavian Cohort • Date of study consent for SoC Cohort
Age	Yes (calculated)	• Year of birth[1]	• Age at Index Date (continuous) • Age groups: 18-40, 41-64, 65+ • Age groups in 5-year increments
Age at HA diagnosis	Yes (calculated)	• Year of birth[1] • Date of diagnosis	• Age at HA diagnosis derived from participant's 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 therapy administration	Yes (calculated)	• Year of birth[1] • Date of the first factor administration	• Age at first FVIII therapy administration derived from participant's year of birth and date of first FVIII administration, unless date of administration is recorded as "unknown"

Variable	Captured in DHR	DHR data field name(s)	Operational definition/description
HTC	--		• Derived from the site associated with study consent and primarily managing a participant • De-identified form based on HTC identifier collected in DHR
Height (within 12 months before index date)	Yes	• Size	• Participant height (cm) • If a participant is missing a height value(s), the nearest height within 12 months before and after the missing height value will be used
Weight (within 12 months before index date)	Yes	• Weight	• Participant weight (kg) • If a participant is missing a weight value(s), the nearest weight within 12 months before and after the missing weight value will be used
BMI (within 12 months before index date)	Yes (calculated)	• Weight; Size	• Calculated field from weight (kg) and height (cm) variables (kg/m^2)[14] o <18.50 (underweight) o 18.50 - <25.00 (normal range) o 25.00 - <30.00 (overweight/pre-obesity) o ≥30.00 (obese) • Categories may be categorized as dichotomous variable (e.g., obese vs. not)
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 • Cured infection – date of the first findings with this result • Active infection – date of the last findings with this result • Eradication treatment carried out	• Not specified • No infection (anti-HCV negative) • Cured infection • Active infection • Presence of acute or uncontrolled chronic hepatic infections at index is an exclusion criterion, which will be confirmed at time of enrollment. HCV status as documented in the DHR will be used to describe the population as well as confirm inclusion/exclusion criteria. • Exclusion criteria will additionally confirmed at time of enrollment based on DHR field confirming that the participant fulfills the AbD inclusion/exclusion criteria.
History of chronic liver disease (ever)	Yes	• Liver disease status • Date liver fibrosis (new diagnosis)	• Not specified • Liver fibrosis (new diagnosis) • Liver fibrosis (chronic) • Liver cirrhosis child A[2] • Liver cirrhosis child B • Liver cirrhosis child C • Liver failure • Categories may be categorized as dichotomous variable (e.g., yes or no)

Variable	Captured in DHR	DHR data field name(s)	Operational definition/description
			• Presence of known significant hepatic fibrosis or cirrhosis at index is an exclusion criterion, which will be confirmed at time of enrollment based on DHR field confirming that the participant fulfills the AbD inclusion/exclusion criteria.
Other comorbidities	Yes	• Other diseases	• Prespecified list of comorbid diseases including: ○ Malignancy: expected to be defined consistently with the safety outcomes ○ Hypertension is sustained elevation of resting systolic blood pressure (≥ 130 mm Hg), diastolic blood pressure (≥ 80 mm Hg), or both[15] ○ Osteoporosis is a progressive metabolic bone disease that decreases bone mineral density (bone mass per unit volume), with deterioration of bone structure. It is defined as DXA results for T-scores ≤ -2.5[16]
Von Willebrand factor	Yes		• Measured in IU/mL
Target joints	Yes	• Localization • Bleeding location	• Yes/No • If localization = "target joint", then target joints will = "yes" • Number and location of target joints will be based on location (shoulder, elbow, hip, knee, ankle joint, or other joint) and side (left, right, not applicable, or unknown) of bleeds identified as "target joint" • For example, if target joint bleeds are recorded at the same location on both sides (e.g., a target joint bleed at the left ankle and a separate target joint bleed at the right ankle), this will be counted as 2 separate target joints. If the target joint location is "other joint" or the side of bleeding is "not applicable or unknown", the number of target joints identified from the bleed will be counted as 1 target joint.
AAV5 antibody status (ever)	Yes	• Have you been tested for AAV antibodies? • If yes: tested serotype • If yes: date • If yes: result (positive/negative)	• Derived from AAV testing for AAV5 being conducted and result of positive/negative
Prophylaxis type	Yes	• Preparation/ medicinal product	• FVIII only • Non-factor products only (e.g., Emicizumab) • FVIII and non-factor products • See Table 4 for drug classifications

Variable	Captured in DHR	DHR data field name(s)	Operational definition/description
Use of immunosuppression (ever)	Yes	• Was immunosuppression performed due to the gene therapy • If yes: drug type immunosuppression	• For participants in Roctavian Cohort, was immunosuppression used (yes/no) • Immunosuppressant drugs based on the DHR specified list of immunosuppressant medications
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 • 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 • Calculate annualized metric of the number of infusions by dividing the number of infusions by the number of days in the relevant time period, multiplied by 365.25
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 (spontaneous 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 (spontaneous hemorrhage), prophylaxis, short-term prophylaxis (intensified on-demand treatment), surgery, ITT, other/unknown
SoC class switching	Yes (calculated)	• Occasion • Preparation/ medicinal product • Therapy start • End of therapy • Start of reporting period • End of reporting period	• Participants who switched between SoC treatments during the 12 months prior to index date (SHL to EHL; SHL to emicizumab; EHL to emicizumab [and vice-versa]; PD to emicizumab). • Participants will be considered to have a switch if occasion = "prophylaxis" for ≥2 different medicinal products identified as SoC treatment classes in Table 4 with therapy dates that do not overlap
Prior ABR (before index date)	Yes (calculated)	• Occasion • Therapy scheme • Severity • Localization	• 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

Variable	Captured in DHR	DHR data field name(s)	Operational definition/description
		• Start of reporting period • End of reporting period	○ Note: a bleeding event is captured if occasion for therapy is spontaneous bleeding/hemorrhage (regardless of severity) • 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; DXA: dual-energy X-ray absorptiometry; FVIII: coagulation factor VIII; HA: hemophilia A; HCV: hepatitis C virus; HTC: hemophilia treatment center; ITT: immune tolerant therapy; IU: international units; kg: kilogram; mm HG: millimeter of mercury; SoC: standard of care

Note: Data fields in the DHR are either mandatory to be entered into the registry per DHR practices or will be monitored to ensure completeness of data for analyses, however responses may still be unknown.

1. Date of birth (month/year) is collected in DHR, but only year is available for analysis per DHR practices. An assumed day and month of birth (01 July) for all participants will be implemented to describe approximate age of participants at index.
2. Progression of fibrosis or cirrhosis will be identified based on recording of an increased Child-Turcotte-Pugh classification (e.g., A → B, B → C) of liver disease relative to liver disease status at baseline or the new diagnosis of cirrhosis.[17-19]

7.4.2. Exposure Variables

Once inclusion and exclusion criteria are applied to the study population, Table 4 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 participant dependent, calculated based on the participant's weight (see Table 3 for weight variable details). 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.

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 as a sensitivity analysis. If treatment switching between SoC classes is observed in >30% of the SoC Cohort, participant characteristics and the primary outcome will be compared between participants 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, participants in the SoC Cohort who are administered Roctavian after study consent will be removed from the analytic dataset.

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 (Octocog alfa)	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 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

Treatment Type	Treatment Class	Treatment Name	Recommended Treatment Frequency and/or Dose
		Efmoroctocog alfa (Elocta)	50 IU/kg every 3-5 days; Dose may be adjusted to 25-65 IU/kg based on response
		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
		Haemate P	One IU of FVIII activity per kg body weight increases the circulating FVIII level by approximately 2.0 IU/dL. Individualize dosage based on weight, type and severity of hemorrhage, FVIII level, and presence of inhibitors.
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 participants 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. Note, all outcomes described below are collected from the index date in both study Cohorts.

Table 5: Outcome Variables

Variable	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 if occasion for therapy is spontaneous bleeding/hemorrhage (regardless of severity)
			• 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 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
				• ≥1 year
				• ≥2 years
				• ≥3 years
				• All available follow-up

Variable	Captured in DHR	DHR data field name(s)	Operational definition and calculation of outcome measures	Timepoints for data collection
			• 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 as treated bleeds (see definition above) with severity recorded as "severe" or "life-threatening" (irrespective of location)
			  ○ Note: a bleeding event is captured if occasion for therapy is spontaneous bleeding/hemorrhage (regardless of severity)
			  ○ Definition of "severe" and "life-threatening" severity will be consistent with existing practices in the DHR[1]
			• 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 as treated bleeds (see definition above) with severity recorded as "life-threatening" (irrespective of location)
			  ○ Note: a bleeding event is captured if occasion for therapy is spontaneous bleeding/hemorrhage (regardless of severity)
			  ○ Life-threatening bleeds will be a subset of treated bleeds and major bleeds
			  ○ Definition of "life-threatening" severity will be consistent with existing practices in the DHR[1]
			• 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

Variable	Captured in DHR	DHR data field name(s)	Operational definition and calculation of outcome measures	Timepoints for data collection
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 as treated bleeds (see definition above) and based on localization of bleed ○ Note: a bleeding event is captured if occasion for therapy is spontaneous bleeding/hemorrhage (regardless of severity) • 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 participants with zero treated bleeds calculated based on treated bleeding • No bleeding events captured within the reporting period start and stop dates • The number of participants within the Cohort with zero treated bleeds is divided by the total number of participants in the 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 • Start of reporting period • End of reporting period	• % Of participants with zero major bleeds calculated based on major bleeding • No bleeding events captured within the reporting period start and stop dates • The number of participants within the Cohort with zero major bleeds is divided by the total number of participants in the Cohort • See definition for major bleed above to be used to derive this variable	• ≥1 year • ≥2 years • ≥3 years • All available follow-up
% Zero life-threatening bleeds	Yes (calculated)	• Occasion • Severity • Start of reporting period • End of reporting period	• % Of participants 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 participants in the Cohort with zero life-threatening bleeds is divided by the total number of participants in the 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

Variable	Captured in DHR	DHR data field name(s)	Operational definition and calculation of outcome measures	Timepoints for data collection
% Zero joint bleeds	Yes (calculated)	• Occasion • Localization • Start of reporting period • End of reporting period	• % Of participants with zero joint bleeds calculated based on joint bleeding • No bleeding events captured within the reporting period start and stop dates • The number of participants in the Cohort with zero joint bleeds is divided by the total number of participants in the 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	• Participants 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 • Consumption/delivery • Treatment date • Start of reporting period • End of reporting period	• Amount of prophylactic hemostatic treatments utilized per participant over time (IU or mg), as well as per participant per kg over time (IU/kg) for FVIII products and mg/kg for emicizumab • Each participant's average weight over the reporting period will be used when calculating IU/kg	• ≥1 year • ≥2 years • ≥3 years • All available follow-up
On-demand hemostatic treatments	Yes (calculated)	• Occasion • Preparation/medicinal product • Weight • Consumption/delivery • Treatment date • Start of reporting period	• Amount of on-demand FVIII utilized per participant over time (IU or mg), as well as per participant per kg over time (IU/kg) for FVIII products and mg/kg for emicizumab for a bleeding event (occasion = "suspected bleeding", "spontaneous bleeding", "traumatic bleeding/bleeding", or "intensified on-demand treatment (=short-term prophylaxis)") • Amount of on-demand FVIII utilized per participant over time (IU or mg), as well as per participant 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

Variable	Captured in DHR	DHR data field name(s)	Operational definition and calculation of outcome measures	Timepoints for data collection
		• End of reporting period	• Each participant's average weight over the reporting period will be used when calculating IU/kg	
FVIII Infusion/ injection rate	Yes (calculated)	• Preparation/ medicinal product • Frequency • Start of reporting period • End of reporting period	• Number of infusions/injections from the index date through the follow-up period • Derived based on the therapy usage and frequency of use during individual usage periods recorded in the DHR for any reason and summarized as AIR	• ≥1 year • ≥2 years • ≥3 years • All available follow-up
Time to resumption of prophylactic treatment	Yes	• Did the patient have to return for prophylaxis? • Date of return to prophylaxis • Date of gene therapy	• Roctavian Cohort only • Derived based on the recording of whether the patient had to return for prophylaxis and if yes, the time (days) between the date of gene therapy and date of return to prophylaxis	All available follow-up
Clinical Outcome Assessments				
HJHS	Yes (calculated)	• Date of the joint score • Score used • Joint score • Score overall movement patten	• For each participant, the HJHS domains are expected to be collected at baseline (index date) and annually 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	Yes		• For each participant, the Haemo-QoL-A questionnaire 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 administration at different time points • Haemo-QoL-A scores are calculated as a total score including all six domains and for each of the six domains separately (physical functioning, role functioning, worry, consequences of bleeding, emotional impact and treatment concerns); Scores will be calculated for the total and each of these six domains	All available follow-up

Variable	Captured in DHR	DHR data field name(s)	Operational definition and calculation of outcome measures	Timepoints for data collection
BPI-sf	Yes		• For each participant, the BPI-sf questionnaire 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 administration at different time points • BPI-sf measures will be reported for pain intensity (Question 5 of BPI-sf that describes participants' pain on average) and pain interference (average of the seven subitems of Question 9 of BPI-sf)	All available follow-up
Safety Outcomes				
All cause death	Yes	• Reason for resignation • Cause of death • Date of retirement	• Any participants with reason for resignation from DHR as "deceased" and cause of death as "hemophilia-related", "non-hemophilia-related", or "unknown"	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	Yes	• Medically relevant events in this reporting period • Relation to hemophilia treatment • Serious consequences due to relevant events	• Identified if serious consequences due to relevant events = "hospitalization" or "death"[2] • Events will be analyzed both for any reason (regardless of relation to hemophilia treatment) and related to hemophilia treatment	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, participants 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 (occasion = "ITT") • Titer (BU/ml) 0.0-1000.0	All available follow-up

Variable	Captured in DHR	DHR data field name(s)	Operational definition and calculation of outcome measures	Timepoints for data collection
		• Occasion		
Thrombo-embolic events	Yes	• Other relevant event • Relation to hemophilia treatment	• Thromboembolic events connected to hemophilia treatment will be identified if other relevant event = "thromboembolic event" and relation to hemophilia treatment = "yes"	All available follow-up
Malignant neoplasms	Yes	• Other relevant event • Relation to hemophilia treatment	• Derived based on recording of medically relevant event of malignant neoplasm in the DHR[3] • Malignant neoplasms connected to hemophilia treatment will be identified if other relevant event = "neoplasm" and relation to hemophilia treatment = "yes" • Occurrence of malignant neoplasm regardless of relationship to treatment will also be described, but not compared • Malignancies are expected to be defined consistent with other data collection occurring in the study population, including the World Federation of Hemophilia Gene Therapy Registry[20, 21]	All available follow-up

Severe liver disease	Yes	• Liver disease status
		• Date of liver fibrosis (new diagnosis)
		• Relation to hemophilia treatment
			• Derived based on recording of liver disease status (liver fibrosis [new diagnosis], liver failure, and liver cirrhosis)
			  ○ Recording during follow-up of "liver fibrosis (new diagnosis)" or "liver failure" will be used to identify events
			  ○ Progression of fibrosis or cirrhosis will be identified based on recording of an increased grade of liver fibrosis/cirrhosis relative to liver disease status at baseline
			  ○ Severe liver disease connected to hemophilia treatment will be identified if relation to hemophilia treatment = "yes"
			  ○ Both events regardless of relationship to hemophilia treatment and specifically related to hemophilia treatment will be analyzed
			• Progression of fibrosis or cirrhosis will be identified based on recording of an increased Child-Turcotte-Pugh classification (e.g., A → B, B → C) of liver disease relative to liver disease status at baseline or the new diagnosis of cirrhosis[17-19]
			• The definition of severe liver disease is consistent with other data collection occurring in the study population, including the international World Federation of Hemophilia Gene Therapy Registry[20, 22]
				All available follow-up

Variable	Captured in DHR	DHR data field name(s)	Operational definition and calculation of outcome measures	Timepoints for data collection
			• Definitions of acute liver failure, liver fibrosis and/or progression of liver fibrosis, or cirrhosis will be consistent with MSD Manuals of classification[17-19]	

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: Data fields in the DHR are either mandatory to be entered into the registry per DHR practices or will be monitored to ensure completeness of data for analyses, however responses may still be unknown.

1. Definition confirmed by DHR as consistent with PedNet. A bleed is classified as severe if the bleed causes pain, swelling, and/or mobility disability and does not end within 24 hours. A bleed is classified as life threatening if the bleed is severe (causes pain, swelling, and/or mobility disability and does not end within 24 hours) and poses a special risk to the patient.
2. Hospitalization defined as a participant having been admitted to the hospital for inpatient care, either to the inpatient ward or to the emergency room for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting.
3. Malignant neoplasms have cells that grow uncontrollably and spread locally and/or to distant sites. Malignant tumors are cancerous (i.e., they invade other sites). They spread to distant sites via the bloodstream or the lymphatic system. This spread is called metastasis. Metastasis can occur anywhere in the body.[23]

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).[24] 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 individuals 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.[25]

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.

Individuals 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 individuals who do not consent, minimal anonymous data is collected. As of 2018, there were 4,240 individuals 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, 26]

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 formula for The sample size calculation is as follows:

$$N_1 \geq \frac{\left(z_\alpha \sqrt{V_0} + z_\beta \sqrt{V_1}\right)^2}{\left(\log(R_0) - \log\left(\lambda_2/\lambda_1\right)\right)^2}$$

$$N_2 = \theta N_1$$

Where:

$$V_1 = \frac{1}{\mu_t}\left(\frac{1}{\lambda_1} + \frac{1}{\theta\lambda_2}\right) + \frac{(1+\theta)\varphi}{\theta}$$

V_0 is computed using the fixed marginal total method, the 2nd method recommended by Zhu et al.:[27]

$$V_{02} = \frac{(1+R_0\theta)^2}{\mu_t R_0\theta(\lambda_1 + \theta\lambda_2)} + \frac{(1+\theta)\varphi}{\theta}$$

N1 is the sample size for control, N2 is the sample size for intervention. $\theta = \frac{N2}{N1}$, which is the sample size ratio; R0 is the superiority margin ratio at the null hypothesis. In this case, R0 is <1 since higher rates are worse. $\lambda 1$ is the event rate in the control group, and $\lambda 2$ is the event rate in the intervention group. φ is the dispersion parameter, and μ_t is the average exposure time. z_α is the z-score at the significance level, z_β is the z-score at the power value.
When higher rates are worse, the superiority by a margin test hypotheses are

$$H_0: \frac{\lambda_2}{\lambda_1} \geq R_0 \quad \text{vs.} \quad H_1: \frac{\lambda_2}{\lambda_1} < R_0$$

Where R0 <1.

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 participants (Roctavian Cohort n = 67, control Cohort n = 330).

Based on current estimates of participant enrollment, the study will be powered based on the ABR approach. The sample size calculation is based on a shifted null hypothesis of 0.5 to add robustness to the generated evidence. Applying and testing a lower shifted null hypothesis (e.g., 0.2) is not feasible to obtain from a physician's perspective and was not agreed upon in the initial sample size discussions with G-BA. In an oral hearing the physicians representing the Gesellschaft für Thrombose und Hämostaseforschung e. V. (GTH) and the Deutschen Gesellschaft für Hämatologie und Medizinische Onkologie e. V. (DGHO) estimated the available population for this study under 700 and only 50% were in single case reporting.[28]
In addition to the shifted null hypothesis, propensity score methodology will be applied to this study design to account for uncertainly in the non-randomized design and ensure the study is more closely approximating randomization.

7.7. Data Management

All data for this study will be collected and stored in the DHR. Study site personnel is responsible for clinical data collection and data entry into the DHR. Validation of clinical 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 Data fields in the DHR (described in sections 7.4.1,7.4.2,and 7.4.3) are either mandatory to be entered into the registry per DHR practices or will be monitored (see section 8.1.2) to ensure completeness of data for analyses. In order to maximize the interpretability of interim analyses, study sites will be asked to enter data specifically for these analyses, which may fall outside of annual reporting at a site. Trained site monitors will provide support to participating sites to minimize the incidence of missing data through routine on-site

monitoring visits and remote routine monitoring visits, tailored to each site depending on the number of participants enrolled and data entry compliance into the DHR.

Furthermore, prior to each planned interim analysis reporting period, site monitors will perform on-site monitoring visits to ensure that all available data has been recorded into the DHR for enrolled participants only.

BioMarin will request data cuts from the DHR at specified intervals to assess data 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 consistent unique identifier based on a de-identified study center code and unique DHR number (e.g., participant 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 participants 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. Considering the intended sample sizes as well as the primary question of interest (e.g., the benefit of Roctavian vs SoC), weighting

methodologies will be preferred and *a priori* the primary analyses will utilize inverse probability of treatment weighting (IPTW). IPTW will utilize all available data compared to matching approaches and estimate the average treatment effect (ATE). Sensitivity analyses will be performed using alternative methods. Propensity score matching (PSM) is planned to be utilized as the main sensitivity method *a priori.* As the primary analysis plans to utilize IPTW and the *a priori* sensitivity analysis is planned to be PSM, these methods have been discussed below in Sections 7.8.3.1 and 7.8.3.2.

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 cohorts. In this section, the methodology of propensity score estimation is described.

Propensity scores will be calculated for participants 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, using backwards stepwise regression, 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 participants 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 6 will be assessed as prespecified candidate covariates for inclusion in the propensity score models. Potential variables for inclusion in the propensity score have been identified based upon variables from a literature review of factors associated with bleeding, previous propensity score development for a comparison of Roctavian to FVIII prophylaxis based on studies that were part of the Roctavian clinical development,[29, 30] and clinical input from health care practitioners (HCPs) in Germany managing PwSHA. Statistical relationships between potential variables and treatment cohorts for the study data, along with clinical input on variables to include regardless of statistical relationship, will be utilized to select variables included in the propensity score.

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 participants in each category level will be presented, as well as the total number of participants with non-missing data for each continuous variable (which by construction will equal the number of participants in the model).

7.8.2. Variable Identification for Propensity Score Model

7.8.2.1. Variable Identification Based on Literature, Previous Work, and Clinical HCP Input

Prior to the initiation of data collection, a comprehensive literature review was conducted to identify the risk factors or covariates associated with bleeding events among PwSHA. No real world data is currently published on characteristics associated with usage of gene therapy compared to other hemostatic therapies. The findings from this review identified a list of potential variables to be assessed in the PS. The comprehensive literature review was designed to capture the most relevant

and high-quality studies based on a fit-for-purpose search strategy developed using key words, medical subject heading (MeSH) terms, and Boolean operators. There were no date or geographic restrictions for the search, but only articles published in English were included. In addition, meeting abstracts were also excluded. After a comprehensive search strategy was developed, the search was executed on November 21, 2023 across the following online databases: Embase, OVID Medline, and the Cochrane Library (CDSR/CENTRAL).

Utilizing the Population, Intervention, Control, Outcome, and Study Design (PICOS) framework, fit-for-purpose study selection criteria was developed. Study selection was conducted in two phases, title/abstract screening, and full-text screening. The initial title and abstract screening was completed by one reviewer (using a conservative approach – including articles that might have missing/unsure PICOS criteria), while subsequent full-text screening was completed by two independent reviewers, where conflicts were resolved between the two reviewers. In addition to the PICOS criteria, only articles that examined the association between HA treatment and bleeding events while considering covariates, either as part of the study design (i.e., pre-randomization stratification or matching) or adjustments in the analysis, were included.

A data extraction form was created, and pilot tested including information on study characteristics, participant characteristics/study population, analysis details, and covariates considered in the study design or analysis of included studies. Once the data extraction form was pilot tested, the first reviewer extracted data based on the presented columns, while the second reviewer verified all the extracted data for quality assurance purposes. After completion of the data extraction, a qualitative synthesis of the included articles was conducted to summarize the articles included in the literature review and to recommend a list of covariates to include in the PS. Overall, the comprehensive literature review included 14 unique studies for covariate assessment (see the protocol for an overview of the literature review results). After HCP expert review, one additional study[31] was also considered to provide recommendations for covariates to include in the PS in order to compliment the results from the comprehensive literature review. This study used predictive modeling to identify predictors of long-term ABR during prophylaxis with EHL FVIII.

In addition to the comprehensive literature review results, HCP expert advice and previous work on developing PS for the comparison of Roctavian to FVIII prophylaxis (as part of the Roctavian clinical development[29]) has informed/confirmed the list of potential variables to assess for inclusion in the PS. In particular, HCPs in Germany treating PwSHA with either Roctavian or SoC products advised the study team regarding overall study conduct and interpretation, as well as providing input into variables identified for PS inclusion. HCPs provided input into variables both associated with the endpoint of bleeding events as well as factors associated with choosing Roctavian treatment.

Table 6 outlines the potential variables to include in the PS based on the comprehensive literature review, expert physician input, and prior comparative Roctavian versus FVIII prophylaxis studies PS development along with considerations for inclusion based on clinical relevance, potential statistical associations, and anticipated correlations between variables. Prior bleeding history, ABR (12 months prior to index date), will be included in the PS regardless of statistical significance due to clinical significance based on feedback from German physicians.

Table 6: List of Potential Variables for Inclusion in PS

Variable	Found by literature review	From previous PS work	Clinical expert opinion	Considerations
Baseline/prior bleeding history (e.g., ABR)	✓	✓	✓	Include regardless of statistical association, based on clinical relevance
Baseline FVIII utilization	✓	✓	✓	Include based on statistical association and correlation with other variables (e.g., baseline/prior bleeding history and baseline prophylaxis class)
Baseline prophylaxis class (FVIII vs. emicizumab)	✓	✓	✓	Include based on statistical association and correlation with other variables (e.g., baseline/prior bleeding history and FVIII utilization)
Age	✓	✓	✓	Include based on statistical association
Height, Weight and/or BMI	✓	✓	✓	Include based on statistical association
Baseline von Willebrand factor (IU/mL)	✓	X	✓	Include based on statistical association
Number of target joints	✓	✓	X	To be considered depending on statistical association and correlation with other variables (e.g., baseline/prior bleeding history and joint health score)
Joint health (e.g., baseline/prior HJHS)	X	X	✓	To be considered depending on statistical association and correlation with other variables (e.g., baseline/prior bleeding history and number of target joints)
Baseline/prior type of bleeds	X	X	✓	To be considered depending on statistical association and correlation with other variables (e.g., baseline/prior bleeding history and target joints)
Geography (HTC/site/region/country)	✓	✓	X	Site to be considered depending on statistical association and correlation with other variables
Prophylaxis class switching (e.g., SHL/PD to EHL/emicizumab)	✓	✓	X	To be considered depending on statistical association and correlation with other variables
Baseline/prior pain (e.g., BPI-sf)	X	X	✓	To be considered depending on statistical association and correlation with other variables (e.g., target joints and HJHS)

Variable	Found by literature review	From previous PS work	Clinical expert opinion	Considerations
Baseline/prior QoL (e.g., haemo-QoL-A)	X	X	✓	To be considered depending on statistical association and correlation with other variables
Activity status	X	X	✓	Not considered as this there is no validated questionnaire for lifestyle factors in PwSHA
Baseline/prior history of liver fibrosis/cirrhosis	✓	X	X	Significant liver fibrosis/cirrhosis is accounted for by the exclusion criteria, but less severe liver fibrosis to be considered based on statistical association
Baseline/prior history of hepatitis B and C	✓	X	X	Not considered as this is accounted for by study exclusion criteria
Baseline/prior history of HIV positivity	✓	X	X	Include based on statistical association
Baseline/prior history of cancer	✓	X	X	Include based on statistical association
Baseline/prior history of hypertension	✓	X	X	Include based on statistical association
Baseline/prior history of osteoporosis	✓	X	X	Include based on statistical association
Adherence to treatment	✓	X	X	Not considered as there is not enough prior literature/evidence to suggest as factor related to bleeding outcomes; confirmed by clinical expert
Genotype	X	X	X	Not considered as this is a factor for inhibitor development but not bleeding outcomes and accounted for by study exclusion criteria for history of or current inhibitors

Abbreviations: ABR: annualized bleeding rate; BMI: body mass index; EHL: extended half-life; FVIII: coagulation factor VIII; HIV: human immunodeficiency virus; HTC: hemophilia treatment center; PD: plasma-derived; PwSHA: people with severe hemophilia A; QoL: quality of life; SHL: standard half-life.

Note: Other variables identified in the literature review but not outlined in Table 6, due to lack of relevance to this study and the association comparing Roctavian and SoC and bleeding outcomes were ethnicity, treatment duration, pharmacokinetic (PK)-guided dosing use, prophylaxis vs on-demand treatment, concurrent medications (bypass agents, non-steroid anti-inflammatory drugs, tranexamic acid, and corticosteroid), and hemophilia severity.

7.8.2.2. Exploration of Unmeasured Confounding

As it may not be feasible to collect all potential variables associated with treatment choice or bleeding outcomes (such as individual lifestyle choices) due to the nature of the study and maximizing data quality for the study when working with an existing registry, it is possible that residual confounding exists as a result of unobserved variables not included in the PS, which could influence the direction and/or magnitude of results observed. Therefore, the E-value, as reported by VanderWeele and Ding, will be used to explore this further.[32]

The E-value is the minimum strength of association, on the risk ratio scale, that an unmeasured confounder would need to have with both the treatment and outcome, conditional on the measured covariates, to explain away a treatment–outcome association. The E-value focuses on the magnitude of the confounder associations that could produce confounding bias equal to the observed treatment–outcome association.

E-value calculations are straightforward. For an observed risk ratio of RR:

E-value = RR + sqrt(RR x (RR – 1))

The formula applies to a risk ratio greater than 1; for a risk ratio less than 1, one first takes the inverse of the observed risk ratio and then applies the formula.

The interpretation of the E-value along with a qualitative assessment, including clinical input from health care practitioners in Germany, will be incorporated into the interpretation of results.

7.8.2.3. Baseline Comparison of Groups for Propensity Score Development

Participant 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.[33] 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 (SMD>0.25) after further refinement of the propensity score model (due to lack of propensity score model convergence) will be removed from the propensity score model and included/adjusted for in the regression model (for model-based analyses – i.e., bleeding events) to estimate the ATE 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,[34, 35] additional analyses will also be performed with the omission of highly correlated variables. Collinearity among covariates that are used to generate weighting from the IPTW 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, an additional 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 IPTW model for the primary outcome. Clinical input will be solicited to select the variable to be retained in the model. In the event a decision cannot be reached using only clinical input, a statistical tiebreaker (Akaike Information Criterion [AIC]) will be used. The model will be run separately with each variable and the model resulting in the lower AIC will be selected. 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, IPTW and PSM methods are described, and considerations for choosing IPTW as the primary analytical method, with PSM as an *a priori* sensitivity analysis are outlined. Propensity score weighting (e.g., IPTW) was chosen as the primary analytical method over PSM since IPTW would include all participants, rather than only those who are successfully matched. Successful matching can be challenging if the study cohort sample sizes are small and therefore, IPTW is recommended. Further, IPTW was chosen over other weighting methods (e.g., standardized mortality ratio weighting [SMRW]) and PSM since the target population is the entire study population, rather than the treatment population. Weighting methods are also subject to extreme weights, IPTW extreme weights can be reduced by using stabilizing weights. Finally, the treatment effect obtained after applying IPTW is referred to as the population ATE, while the resulting treatment effect obtained from SMRW is the average treatment effect on the treated (ATT) population. The ATE is more applicable for this study, since the Roctavian treatment may be offered to any participant eligible for the study and is not dependent on participant characteristics.[36] PSM is chosen as the *a priori* sensitivity analysis as it is commonly used in observational studies to balance the study groups while randomization is implausible. It provides subject-to-subject comparison by reducing the multi-dimensional covariate space to one dimension space and the results are easy to interpret.[37] As the primary analysis will utilize IPTW and PSM as an *a priori* sensitivity analysis, these approaches are summarized below in Table 7 and more details are provided around these approaches in Sections 7.8.3.1 and 7.8.3.2.

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

Table 7: Considerations for IPTW versus PSM Methods

Propensity Score Method	Considerations
IPTW	• Includes all participants • Applies weights to both the treated and control cohorts • Estimates the ATE in the total study population • Subject to extreme weighting
PSM	• Only includes 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: ATE: average treatment effect; IPTW: inverse probability of treatment weighting; PSM: propensity score model.

7.8.3.1. Inverse Probability of Treatment Weighting

IPTW will be implemented to create a baseline reference of propensity score weights for comparison. Using this approach, each participant is assigned a weight representing the inverse probability of being assigned to their respective group. Thus, IPTW aims at giving more importance (i.e., more "weight") to those participants that have unexpected propensity score values. For the treated group

(Roctavian Cohort), the weight, W, assigned in the IPTW method for each individual, i, based on propensity score, P_i, is:

$$W_i = \frac{1}{P_i}$$

For the control group (SoC Cohort), participants receive weights of:

$$W_i = \frac{1}{(1 - P_i)}$$

As the characteristics of the population that will be treated with Roctavian are unknown at the time of the SAP being drafted, it is possible that large differences in characteristics between the Roctavian and SoC Cohorts will exist. If this is the case, some participants may have extreme propensity score weights and, though representing a small portion of the observed population, have a disproportionate influence on the analysis. This outsized influence of individuals with extreme weights may increase variance and confidence intervals of the ATE estimate.[38]

Stabilized weights can be used instead of the original, unstabilized weights. To calculate the stabilized weights, the numerator of the unstabilized weights is replaced by the marginal probability of receiving Roctavian and SoC in the overall sample. Additionally, weight values greater than five will be truncated to five due to the potential bias of outliers.[39, 40]

For the Roctavian Cohort, the stabilized weight, W, assigned in the IPTW method for each individual i, is obtained by dividing the marginal probability of receiving Roctavian (i.e., a propensity score without considering covariates) P_T by individual's propensity score, P_i,:

$$W_i = \frac{P_T}{P_i}$$

For the SoC Cohort, participants receive weights of:

$$W_i = \frac{(1 - P_T)}{(1 - P_i)}$$

We will conduct trimming of the nonoverlap regions of PS if extreme weights still exist with stabilized IPTW.[41, 42] If the IPTW requires trimming due to extreme weighting to balance the propensity score distributions between the Roctavian and SoC Cohorts, and if the PSM sensitivity analysis can match a sufficient sample size to incorporate a 1:1 or 1:2 matching ratio (see Section 7.8.3.2 for details), the PSM approach will be reported as the primary analytical method for all analyses.

7.8.3.2. Propensity Score Matching

PSM will be considered *a priori* for a sensitivity analysis and initially be performed using the procedure of 1:4 matching. The PSM method matches each subject in the treated Cohort with four subjects in the SoC Cohort exhibiting the nearest propensity score (this is also known colloquially as 'greedy' matching) without replacement. Consequently, if all participants from the smallest group (i.e., Roctavian or SoC) are matched, then the sample size for the participants included in subsequent analysis becomes double the sample size of the smallest group of unpaired participants. If the appropriate matches are 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. For the PSM, a caliper width of 0.2 times the SD of the propensity score will be used and 'random' order.[43]

If the 1:4 matching ratio is not achievable at the specified caliper with >90% of the Roctavian Cohort matched to four SoC participants, a 1:3 matching ratio will be attempted, followed by a 1:2 matching ratio and then a 1:1 matching ratio as needed based on the requirement to match >90% to the

relevant ratio. If the 1:1 matching ratio is not achievable, results for PSM will not be reported. Between IPTW and PSM, it is expected that one of these methods would have sufficient overlap and model fit to use for analyses, however if they don't, multivariable regression analyses with covariate adjustment will be conducted with discussion and agreement from the G-BA.

PSM will be conducted for the primary outcome and compared to the results using IPTW. If there is no notable difference in the primary outcome, only IPTW will be used for the secondary outcomes.

7.8.3.3. 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 to visually assess any imbalance (i.e., to visually determine sufficient overlap between the two curves). Balance plots for the participant 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 (see Section 7.9.3 for details). 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 IPTW is applied) and the weighted values (after IPTW is applied).

To adjust for confounding, propensity scores will be calculated and applied using appropriate propensity score IPTW to ensure balance of covariates between the Roctavian and SoC Cohorts. Both unadjusted and propensity score adjusted results will be reported. IPTW is the primary propensity score method for adjustment of confounding. PSM will be performed as an *a priori* sensitivity analysis. Additional details on propensity score methodology is presented in Section 7.8. 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. The sample size calculations are powered for the primary outcome (i.e., ABR), therefore, all p-values associated with secondary outcomes are nominal.

7.9.1. Participant Attrition

Participants 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[44] will be used to visualize sample size for the study population and cohort assignment.

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 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 participants (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 participants 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.[45]

Participant characteristics will be presented for all participants prior to weighting and after weighting (for Roctavian and SoC Cohorts separately), overall, and for subgroups and sensitivity analyses where appropriate. Participant characteristics prior to and after weighting will be compared using the statistical tests noted above to capture differences between the observed population and the weighted target population.

7.9.3. Analysis of Primary Outcome

Population	Measurement Period	Analysis Notes
All participants 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	Participants 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 and Roctavian Cohorts. Bleeds will be identified if participants have an "occasion" for treatment of spontaneous bleeding/hemorrhage (regardless of severity). Participants may have multiple bleeds during the reporting period. To calculate ABR, a count of the number of bleeds for each participant will be divided by the number of days in the relevant time period for each participant, 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 participants 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.

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 participant number in the two Cohorts will be weighted using IPTW 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 IPTW weighted negative binomial model will be fit to compare ABR between Roctavian and SoC Cohort, with negative binomial distribution and log link function, and the log transformed follow-up time as the offset variable. IPTW will be applied to create

more similar Roctavian and SoC Cohorts. 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. The estimated rate ratio (ABR in Roctavian Cohort / ABR in SoC Cohort) generated from the IPTW weighted negative binomial model will be tested against the shifted null hypothesis of 0.5. For an alpha=0.025 test, the shifted null hypothesis is rejected if the upper boundary of the two-sided 95% CI for the rate ratio is less than the null hypothesis 0.5. The CI of the estimated rate ratio will be calculated using the Wald method.[27]

Given some participants may have no treated bleeds based on prior literature,[46] a two-part zero-inflated negative binomial model will also be considered. If the negative binomial model does not converge,[47] or if the AIC in the model accounting for zero-inflation is lower, then the zero-inflation negative binomial model will become the primary objective analytic model, as lower AIC indicates a better fit. For the zero-inflated negative binomial model, first the model will be fit for a binary outcome whether a participant had a treated bleed during the outcome assessment period, and then an ABR count outcome for treated bleeds among participants who had at least one treated bleed during the outcome assessment period (excluding participants 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, COAs, 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 participants 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	Participants 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 participants in that Cohort, multiplied by 365.25. ABR of each Cohort will be compared over the full follow-up time for each participant in the study, as well as during annual increments during the follow-up period.

Similar to the analytic approach for the primary outcome, an IPTW weighted negative binomial model or a IPTW weighted zero-inflated negative binomial model, whichever appropriate (based on the rules applied in the primary objective Section 7.9.3), will be fit to compare each ABR measure between Roctavian and SoC Cohorts. IPTW will be applied to create more similar Roctavian and SoC Cohorts. 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 Participants with Zero Bleeds

Population	Measurement Period
All participants	≥1 year of follow-up, ≥2 years of follow-up, ≥3 years of follow-up, all available follow-up

For interim and analyses at fixed timepoints, only those with specified amounts of follow-up will be included	

The proportion of participants 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 (IPTW), analysis of the full follow-up period along with annual increments and start of follow-up period.

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

7.9.4.3. Use of Hemostatic Medications

Population	Measurement Period	Analysis Notes
All participants 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	Participants 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 participants using FVIII treatments and participants using emicizumab. They will separately be compared to the Roctavian Cohort. The amount of total (prophylactic and on-demand) treatments utilized per participant 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). Each participant's average weight over the reporting period will be used when calculating IU/kg. Prophylaxis and on-demand use will be described as available.

The proportion of participants 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 participants 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 participants 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 participants 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 IPTW 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 participants with sufficient follow-up, comparing Roctavian Cohort to SoC Cohort; Participants without any COA scores will not be included	Assessments are expected to be conducted at baseline and every 6 months for quality of life and pain, and for joint health at least annually	For analyses of change from baseline, participants 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 as 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. Physicians participating in the AbD are expected to enter data for these instruments collected relative to the study index date per the operational definitions outlined in Table 5. The following Table 8 includes the assessment timepoints of interest throughout the follow-up and tolerance windows. If a participant has multiple measurements reported in the same window, the measurement closest to the time point of interest will be selected. An individual data point will only be utilized once in the analysis (e.g., if there is a measure at 1.2 years, this data point would only be used for 1 year and not the 2 year analysis).

Table 8. COA Timepoints of Interest and Tolerance Windows

Timepoints of Interest	Day of Assessment	Tolerance Window[1]
Baseline	Index date, day 0	0-91 days
6-months	Day 182	92-273 days
12-months (1 year)	Day 365	274-456 days
18-months	Day 547	457-638 days
24-months (2 years)	Day 730	639-821 days
30-months	Day 912	822-1,003 days
36-months (3 years)	Day 1,095	1,004-1,185 days

1. Tolerance windows are +/- 3 months before and after the expected assessment day.

Note: HJHS assessments will be completely annually, while Haemo-QoL-A and BPI-sf assessments will be completed every 6 months.

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 as the effect size measure.[48] 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.

Participants with an evaluable baseline score and at least one evaluable post-baseline score will be included in the change from baseline analyses. Since participants are expected to have follow-up visits every 6-months for Haemo-QoL-A and BPI-sf and annual follow-up visits for HJHS, it is expected that COAs will be measured with a maximum of seven time points for Haemo-QoL-A and BPI-sf (baseline, 6±3, 12±3, 18±3, 24±3, 30±3, and 36±3 months) and four time points (baseline, 12±3, 24±3, and 36±3 months) for HJHS. The last follow-up measure will be used in the change from baseline analysis. 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. Regression coefficients, 95% CIs and P-values for each of the fixed-effects parameters will be reported. Estimated correlation matrix will also be reported to assess the correlation of the outcome between each time point.

For all the COA outcomes described above, both the unweighted and IPTW 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.

In addition, a responder analysis will be considered for the COA improvement and deterioration of the six joint health 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.[49] Based on IQWiG's guidance for responder analysis, (a 15% change of the scale range)[50], participants 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 participants will be defined as non-responders. The binary outcome (responder versus not) will be analyzed using propensity score IPTW weighted log binomial regression models. The main predictor of interest is the treatment effect (Roctavian vs. SoC), other imbalanced covariates after propensity score adjustment may be included in the model as necessary. The risk ratio (relative risk), corresponding 95% CIs and p-values will be reported.

To visually represent the responder analysis results and to aid in its interpretation, The response rate at each time point will be plotted as response curves for each COA by study Cohort to illustrate the change in response rate across time.

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.[51] 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 participant'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 participants receiving both prophylactic and on-demand therapy.[52] 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). Participants 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 participants 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 participants 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 rates are defined as the number of participants who have the baseline measure and at least one post-baseline measure (to be calculated at all timepoints of interest including 12-months, 24-months and 36-months), divided by the total number of enrolled participants. The full completion rate is defined as number of participants who have the baseline measure and all post-baseline measures, divided by the total number of enrolled participants.

The analytical techniques described in Section 7.9.4.4 will be applied to the HJHS outcomes including descriptive statistics, change from baseline analyses, repeated measures model analyses, and responder analyses. Please refer to Section 7.9.4.4 for details.

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.[53] 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 participants 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.[54] 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). Participants 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 participants 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 participants 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 participants who have the baseline measure and at least one post-baseline measure (to be calculated at all timepoints of interest, including 6-months, 12-months, 18-months, 24-months, 30-months, and 36-months), divided by the total number of enrolled participants. The full completion rate is defined as number of participants who have the baseline measure and all post-baseline measures, divided by the total number of enrolled participants.

The analytical techniques described in Section 7.9.4.4 will be applied to the Haemo-QoL-A outcomes including descriptive statistics, change from baseline analyses, repeated measures model analyses, and responder analyses. Please refer to Section 7.9.4.4 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).[55] The BPI-SF measures generic pain (i.e., is not indication-specific) has been used and validated in hemophilia.[56-58]

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). Participants 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 participants 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 participants 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 participants who have the baseline measure and at least one post-baseline measure (to be calculated at all timepoints of interest, including 6-months, 12-months, 18-months, 24-months, 30-months, and 36-months), divided by the total number of enrolled participants. The full completion rate is defined as number of participants who have the baseline measure and all post-baseline measures, divided by the total number of enrolled participants.

The analytical techniques described in Section 7.9.4.4 will be applied to the BPI-sf outcomes including descriptive statistics, change from baseline analyses, repeated measures model analyses, and responder analyses. Please refer to Section 7.9.4.4 for details.

7.9.4.5. Safety Events

Population	Measurement Period	Analysis Notes
All participants	All available follow-up data	Safety events will be compared between the Roctavian and SoC Cohorts Due to the possibility of unknown responses, there may be insufficient data to fully describe participant comorbidities that may confound the 'true' causal reason for an event.

Safety events outlined in Table 5 will be reported for both the Roctavian and SoC Cohorts.

Regarding the treatment policy estimand data analysis, the proportion of participants with each event will be calculated from index through the full follow-up period, without considering any intercurrent events. Given safety outcomes are event-based, for safety outcomes occur multiple times over the follow-up period (e.g., thromboembolic events), IPTW-weighted negative binomial regression models will be fit to compare safety outcomes between Roctavian and SoC Cohorts. For safety outcomes expected to occur once (e.g., death), IPTW-weighted log binomial regression models will be fit to compare safety outcomes between Roctavian and SoC Cohorts.

IPTW will be applied to create more similar Roctavian and SoC Cohorts. 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. In the case that there are little to no events n<10, that the relative risk log-binomial regression or negative binomial regression estimates are not stable, a logistic regression (which can approximate relative risk in a rare outcome[59]) with firth correction will be conducted.

Under the hypothetical estimand data analysis, the event rate and incidence rate of each event will be calculated from index through the full follow-up period, where all participants will be included in analyses of event or incidence rates. Further, to compare Roctavian and SoC Cohorts safety outcomes under the hypothetical estimand, IPTW-weighted incident rate ratios (IRRs) will be estimated at the incident/event rate among the Roctavian Cohort divided by the incident/event rate among the SoC Cohort. 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.

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 participants in the Roctavian Cohort, time to resumption of prophylactic treatment will be measured for participants who received SoC prophylaxis after Roctavian administration during the follow-up period. Treatment utilization patterns in the 3 and 6 months after the resumption of prophylaxis will be described regarding the number of infusions/injections by prophylaxis treatment class, total FVIII dose for participants returning to prophylaxis with FVIII, and frequency of infusions/injections. Summary statistics will be utilized to describe time to resumption including mean, SD, median, IQR, minimum, and maximum.

7.9.5. Other Analyses

Per the resolution requiring the Routine Data Collection and Evaluations for Valoctocogene Roxaparvovec,[60] additional analyses comparing outcomes between the Roctavian Cohort and classes of SoC prophylaxis (FVIII products and emicizumab), age groups, as well as for the SoC Cohort AAV 5 antibody status 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 for subgroups will be described during the 18-month interim report, though analyses are planned *a priori*. 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 characteristics of the sub-Cohort, which will impact the ability of the PS to address confounding, as well as sample size. 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 PwSHA 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 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 sub-group analyses for the primary objective, but not for secondary objectives due to missing data). It is assumed *a priori* that analyses will be feasible.

Baseline characteristics and all primary and secondary outcomes (as appropriate) will be reported (using the same analytic methods as described above) for the following analyses:

SoC Cohort Prophylaxis Treatment Type Subgroup Analysis

- Participants 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 participant receives at study consent will only be captured in this analysis, any treatment switch after consent will not be captured by this analysis.
- Each prophylaxis-specific subgroup will be described and compared to the Roctavian Cohort separately as sample size permits.

- A likelihood ratio test will be applied to examine if the SoC treatment types are statistically significantly different.

Age Group Subgroup Analysis

- Participants in both Roctavian and SoC Cohorts will be stratified on age at index date in the following groupings: 18-40, 41-64, 65+.

- A likelihood ratio test will be applied to examine if age groups are statistically significant different across the primary and secondary objective results.

AAV5 Antibody Status Subgroup Analysis

- The study results will be stratified by participants 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 testing in clinical practice among the SOC cohort.

SoC Switching Sensitivity Analysis

- The study results will be reported for participants in the SoC Cohort who receive Roctavian during the follow-up period and are censored at the time of switching.

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 = “spontaneous hemorrhage”).

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 participants 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 participants in the SoC Cohort who stay on the same class of treatment throughout the duration of the follow-up period.

7.9.5.1. Missing Data Analyses

Source data verification will aid in the reduction of missing, or incomplete data in the DHR. Due to the non-interventional nature of this data collection, complete avoidance of missing or implausible data is impossible, however minimal missing data is expected as fields in the DHR will be mandatory or monitored to ensure completeness of the data for analysis. Therefore, 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 participants with and without missing data will be compared among participants with complete data versus those with any missing data. Missing data imputation will be considered based on the presence of patterns of missingness and effect of missing data on the interpretability of the results. If a covariate is included in the propensity score model and has more than 40% missingness, that covariate will be excluded from the propensity score model. However, among *a priori* selected covariates in the propensity score model with less than 40% missing data, multiple imputation applying the fully conditional specification method (FCS) will be used.[61] The FCS method, also called chain equations method, imputes missing data in a dataset through an iterative series of predictive models. In each iteration, the specified variable is imputed

using other variables in the dataset. FCS is a flexible multiple imputation method and can handle various types of variables, such as binary, ordinary, or continuous variables.[62] Categorical variables will be imputed using the discriminant function, continuous variables using ordinary linear regression, ordinal variables using ordinal logistic regression, and binary variables using logistic regression.

Missing data imputation will be conducted for missing month (to derive age) however, other data fields will not be imputed. An assumed day and month of birth (01 July) for all participants will be implemented to describe approximate age of participants at index.

7.9.6. Interim Analysis

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

At the 18-month interim analysis, the Roctavian and SoC Cohorts will be described, the propensity scores will be built and assessed for performance, and all outcome analyses will be descriptively reported. Among participants that have at least one year of follow-up, comparative analyses will be performed. The 18-month interim analysis will also evaluate the number of enrolled participants 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 participants.

Study sites will be asked to update data for all AbD participants approximately 6 months prior to each planned interim analysis and will be supported by site monitors through on-site monitoring and routine monitoring visits to ensure that all available data for enrolled participants are recorded into the DHR prior to the planned interim analysis.

7.9.6.1. Futility Analysis

A futility analysis will be conducted at the 18-month interim analysis to assess whether the study should be terminated early due to the inability to meet the required sample size for comparative analyses. Discontinuation criteria for the study will involve if either of the following conditions are met (unless there is an indication that recruitment is expected to considerably increase during the remainder of the recruitment period) at the 18-month interim analysis/report:

- Roctavian Cohort is expected to include ≤33 persons (<50% of the target sample size for the Roctavian Cohort)
- SoC Cohort is expected to include <67 persons (target sample size of the Roctavian Cohort)

Based on these discontinuation criteria, the futility analysis will examine the total number of participants enrolled in the study, the number of participants in each of the SoC and Roctavian Cohorts and the amount of time remaining in the study recruitment window. Assessments of potential futility and implications on study interpretation will be discussed in the reports associated with these interim analyses.

A futility assessment will also be included as part of the 36-month and 54-month interim analyses to determine the observed ABR of each Cohort. The sample size calculation conducted *a priori* (see section 7.6) will be re-calculated based on the observed ABR of each cohort at these timepoints. Implications on study interpretation will be discussed in the reports associated with these interim analyses.

Continued conduct of the study as described in the original study protocol based on the futility assessment at these timepoints will be discussed with the G-BA. Any changes to the conduct of the study and AbD based on the futility assessment will be made in agreement 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., participant weight <10 kg, participant with >50 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.[63]

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. Participants 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 participant randomization, Roctavian and SoC therapies may be prescribed to groups of participants 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.
    - In addition to variables that are not feasible to capture in an observational registry, the non-interventional nature of the study reflecting a range of real-world practice in Germany could introduce confounding that cannot be fully addressed with PS or specific applications of the PS (e.g. matching). For example, PwSHA are recommended to be treated with hemostatic prophylaxis, though a small portion of the severe hemophilia A population in Germany may still be utilizing an on-demand treatment regimen. Persons utilizing an on-demand regimen are likely to have a higher baseline bleeding rate, as prophylaxis is associated with reduced bleeding events. All persons administered commercially available Roctavian are expected to have received hemostatic prophylaxis treatment for at least 12 months by the time that a participant will be treated with Roctavian gene therapy. If persons treated with an on-demand regimen for part of the baseline period enroll into the SOC Cohort, these participants may have outlier propensity scores which may not be able to be matched. The proportion of on-demand participants in the SOC Cohort, as well as impact of these participants on the analysis will be discussed in interim and final reports.
- **Loss to follow-up**: Participant retention through the end of the expected observation period will be monitored carefully and attempts will be made to obtain follow-up data from participants who discontinue treatment. However, some participants may have fewer than three years of follow-up data available. Participants in the SoC Cohort are expected to have follow-up twice per year whereas participants 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 participants. 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 one 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, 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,[64] the International Society for Pharmacoepidemiology Guidelines for Good Pharmacoepidemiology Practices (GPP),[65] 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 may not be recorded in the data source (i.e., AbD).

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. Monitoring of safety data via on-site and remote monitoring visits as described in the protocol will be utilized to ensure that relevant targeted AEs 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 medicinal products and devices to the relevant competent authority.[66]

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/clinical 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/.

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12. Annexes

12.1. Table Shells

All table shells will be populated for the treatment policy estimand. Then the table shells will be adjusted and populated for the hypothetical estimand data analysis, as well as the other sensitivity and subgroup analyses discussed in Section 7.9.5

Table 1 Sample Attrition for Roctavian and SoC Cohorts

		Roctavian Cohort				SoC Cohort			
		Excluded		Remaining		Excluded		Remaining	
Step #	Attrition steps (to be applied sequentially)	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 (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%
6	With no presence of acute or uncontrolled chronic infections, and/or known significant hepatic fibrosis or cirrhosis at index	0	0.00%	0	0.00%	0	0.00%	0	0.00%
	Final Cohorts			0				0	

Data source: DHR from the start of data collection accompanying the application to approximately 6 months prior to the date of the final report required by the G-BA resolution for AbD

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 IPTW					
	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			
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 IPTW					
	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 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 the start of data collection accompanying the application to approximately 6 months prior to the date of the final report required by the G-BA resolution for AbD

Acronyms: SoC: standard of care; SD: standard deviation; FVIII: coagulation factor VIII; HA: hemophilia A; HTC: hemophilia treatment center

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 IPTW					
	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
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%		

Measures	Unadjusted						After IPTW					
	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	(%)		
Other comorbidities												
Malignancy	0	0.0%	0	0.0%	0.0000	0.00	0	0.0%	0	0.0%	0.0000	0.00
Hypertension	0	0.0%	0	0.0%			0	0.0%	0	0.0%		
Osteoporosis	0	0.0%	0	0.0%			0	0.0%	0	0.0%		
Von Willebrand factor (IU/mL)												
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			
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
Non-factor products only (e.g., emicizumab)	0	0.0%	0	0.0%			0	0.0%	0	0.0%		
FVIII and non-factor products	0	0.0%	0	0.0%			0	0.0%	0	0.0%		
SoC switch	0	0.0%	0	0.0%	0.0000	0.00	0	0.0%	0	0.0%	0.0000	0.00
SHL to EHL	0	0.0%	0	0.0%	0.0000	0.00	0	0.0%	0	0.0%	0.0000	0.00

Measures	Unadjusted						After IPTW					
	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	(%)		
SHL to emicizumab	0	0.0%	0	0.0%	0.0000	0.00	0	0.0%	0	0.0%	0.0000	0.00
EHL to emicizumab	0	0.0%	0	0.0%	0.0000	0.00	0	0.0%	0	0.0%	0.0000	0.00
Emicizumab to SHL	0	0.0%	0	0.0%	0.0000	0.00	0	0.0%	0	0.0%	0.0000	0.00
Emicizumab to EHL	0	0.0%	0	0.0%	0.0000	0.00	0	0.0%	0	0.0%	0.0000	0.00
Emicizumab to PD	0	0.0%	0	0.0%	0.0000	0.00	0	0.0%	0	0.0%	0.0000	0.00
PD to emicizumab	0	0.0%	0	0.0%	0.0000	0.00	0	0.0%	0	0.0%	0.0000	0.00
AAV5 antibody status												
AAV5 Tab-	0	0.0%					0	0.0%				
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			

Measures	Unadjusted						After IPTW					
	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	(%)		
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	
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

Measures	Unadjusted						After IPTW					
	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			
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			
Min	0		0				0		0			
Max	0		0				0		0			

Measures	Unadjusted						After IPTW					
	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	(%)		
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			
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			

Measures	Unadjusted						After IPTW					
	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 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 the start of data collection accompanying the application to approximately 6 months prior to the date of the final report required by the G-BA resolution for AbD

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: 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 prior to start of data collection.

Table 5 ABR for Roctavian and SoC Cohorts

Measures	Unadjusted				After IPTW			
	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		
Median	0	0	0.0000		0	0	0.0000	
Q1	0	0			0	0		
Q3	0	0			0	0		

Measures	Unadjusted				After IPTW			
	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)
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		
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		

Measures	Unadjusted				After IPTW			
	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)
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		
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		

Measures	Unadjusted				After IPTW			
	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		
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
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		

Measures	Unadjusted				After IPTW			
	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		

Data source: DHR from the start of data collection accompanying the application to approximately 6 months prior to the date of the final report required by the G-BA resolution for AbD

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 IPTW-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 the start of data collection accompanying the application to approximately 6 months prior to the date of the final report required by the G-BA resolution for AbD
Acronyms: SoC: standard of care

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

Measures	Unadjusted						After IPTW					
	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	(%)		
Participants 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
Participants 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
Participants 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
Participants 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 the start of data collection accompanying the application to approximately 6 months prior to the date of the final report required by the G-BA resolution for AbD

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 IPTW-Adjusted Logistic Regression Model of Participants with Zero Bleeds for the Overall Timeframe, Roctavian and SoC Cohorts

Unadjusted Logistic Regression Model

Measures	Risk 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	Risk 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 the start of data collection accompanying the application to approximately 6 months prior to the date of the final report required by the G-BA resolution for AbD
Acronyms: SoC: standard of care

Table 9 Hemostatic Medication Use for Roctavian and SoC Cohorts

Measures	Unadjusted										After IPTW									
	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	(%)		
Participants 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 %		
Participants 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		0.0		0.0000	0.00	0.00		0.00		0.00		0.0		0.0000	0.00
SD	0.00		0.00		0.00		0.0				0.00		0.00		0.00		0.0			
Median	0		0		0		0		0.0000		0		0		0		0		0.0000	
Q1	0		0		0		0				0		0		0		0			

Measures	Unadjusted										After IPTW									
	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	(%)		
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			
Total prophylactic FVIII utilization per participant 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			

Measures	Unadjusted										After IPTW									
	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			
Total prophylactic emicizumab utilization (mg)																				
Mean	0.00		0.00		0.00		0.0		0.0000	0.00	0.00		0.00		0.00		0.0		0.0000	0.00
SD	0.00		0.00		0.00		0.0				0.00		0.00		0.00		0.0			
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 participant per kg (mg/kg)																				
Mean	0.00		0.00		0.00		0.0		0.0000	0.00	0.00		0.00		0.00		0.0		0.0000	0.00
SD	0.00		0.00		0.00		0.0				0.00		0.00		0.00		0.0			
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)																				

Measures	Unadjusted										After IPTW									
	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	(%)		
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 participant 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			
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			

Measures	Unadjusted										After IPTW									
	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 per participant 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
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 participant 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			

Measures	Unadjusted										After IPTW									
	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			
Total on-demand emicizumab utilization for short-term prophylaxis (mg)																				
Mean	0.00		0.00		0.00		0.0		0.0000	0.00	0.00		0.00		0.00		0.0		0.0000	0.00
SD	0.00		0.00		0.00		0.0				0.00		0.00		0.00		0.0			
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 participant per kg for short-term prophylaxis (mg/kg)																				
Mean	0.00		0.00		0.00		0.0		0.0000	0.00	0.00		0.00		0.00		0.0		0.0000	0.00
SD	0.00		0.00		0.00		0.0				0.00		0.00		0.00		0.0			
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 the start of data collection accompanying the application to approximately 6 months prior to the date of the final report required by the G-BA resolution for AbD

Measures	Unadjusted										After IPTW									
	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	(%)		

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 IPTW					
	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												
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			

Measures	Unadjusted						After IPTW					
	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			
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	

Measures	Unadjusted						After IPTW					
	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			
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

Measures	Unadjusted						After IPTW					
	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	(%)		
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			
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

Measures	Unadjusted						After IPTW					
	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	(%)		
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			
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			

Measures	Unadjusted						After IPTW					
	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 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			
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			

Measures	Unadjusted						After IPTW					
	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	(%)		
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			

Data source: DHR from the start of data collection accompanying the application to approximately 6 months prior to the date of the final report required by the G-BA resolution for AbD

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 IPTW					
	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	
Q1	0		0				0		0			
Q3	0		0				0		0			
Min	0		0				0		0			
Max	0		0				0		0			

	Unadjusted						After IPTW					
	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	(%)		
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
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 IPTW					
	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	(%)		
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	
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

	Unadjusted						After IPTW					
	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	(%)		
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			
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

	Unadjusted						After IPTW					
	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	(%)		
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	
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			

	Unadjusted						After IPTW					
	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	(%)		
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 the start of data collection accompanying the application to approximately 6 months prior to the date of the final report required by the G-BA resolution for AbD

Acronyms: SoC: standard of care; COA: clinical outcome assessment; 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 12 COAs for Roctavian and SoC Cohorts – BPI-sf

Measures	Unadjusted						After IPTW					
	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			
Q3	0		0				0		0			
Min	0		0				0		0			
Max	0		0				0		0			

Measures	Unadjusted						After IPTW					
	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	(%)		
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
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 IPTW					
	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	(%)		
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			
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			

Measures	Unadjusted						After IPTW					
	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	(%)		
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			
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 IPTW					
	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	(%)		

Data source: DHR from the start of data collection accompanying the application to approximately 6 months prior to the date of the final report required by the G-BA resolution for AbD

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 IPTW-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 the start of data collection accompanying the application to approximately 6 months prior to the date of the final report required by the G-BA resolution for AbD

Acronyms: COA: clinical outcome assessment; SoC: standard of care; HJHS: Hemophilia Joint Health Score; BPI-sf: Brief Pain Inventory – short form

Table 14 Responder Analyses

HJHS Responder Analysis – Participants with ≥15% improvement in HJHS

Measures	Unadjusted					After IPTW				
	Roctavian Cohort N=		SoC Cohort N=		p-value (Roctavian vs. SoC)	Roctavian Cohort N=		SoC Cohort N=		p-value (Roctavian vs. SoC)
	N	(%)	N	(%)		N	(%)	N	(%)	
Left elbow	0	0.0%	0	0.0%	0.0000	0	0.0%	0	0.0%	0.0000
Right elbow	0	0.0%	0	0.0%	0.0000	0	0.0%	0	0.0%	0.0000
Left knee	0	0.0%	0	0.0%	0.0000	0	0.0%	0	0.0%	0.0000
Right knee	0	0.0%	0	0.0%	0.0000	0	0.0%	0	0.0%	0.0000
Left ankle	0	0.0%	0	0.0%	0.0000	0	0.0%	0	0.0%	0.0000
Right ankle	0	0.0%	0	0.0%	0.0000	0	0.0%	0	0.0%	0.0000
Global gait score	0	0.0%	0	0.0%	0.0000	0	0.0%	0	0.0%	0.0000

HJHS Responder Analysis - Participants with ≥15% deterioration in HJHS

Measures	Unadjusted					After IPTW				
	Roctavian Cohort N=		SoC Cohort N=		p-value (Roctavian vs. SoC)	Roctavian Cohort N=		SoC Cohort N=		p-value (Roctavian vs. SoC)
	N	(%)	N	(%)		N	(%)	N	(%)	

Left elbow	0	0.0%	0	0.0%	0.0000	0	0.0%	0	0.0%	0.0000
Right elbow	0	0.0%	0	0.0%	0.0000	0	0.0%	0	0.0%	0.0000
Left knee	0	0.0%	0	0.0%	0.0000	0	0.0%	0	0.0%	0.0000
Right knee	0	0.0%	0	0.0%	0.0000	0	0.0%	0	0.0%	0.0000
Left ankle	0	0.0%	0	0.0%	0.0000	0	0.0%	0	0.0%	0.0000
Right ankle	0	0.0%	0	0.0%	0.0000	0	0.0%	0	0.0%	0.0000
Global gait score	0	0.0%	0	0.0%	0.0000	0	0.0%	0	0.0%	0.0000

Data source: DHR from the start of data collection accompanying the application to approximately 6 months prior to the date of the final report required by the G-BA resolution for AbD
Acronyms: HJHS: Hemophilia Joint Health Score; SoC: standard of care

HJHS Progression Curve of Responder Analysis - Participants with ≥15% deterioration in HJHS

Haemo-QoL-A Responder Analysis – Participants with ≥15% improvement in Haemo-QoL-A scores

Measures	Unadjusted					After IPTW				
	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	(%)	
Physical functioning	0	0.0%	0	0.0%	0.0000	0	0.0%	0	0.0%	0.0000

Role functioning	0	0.0%	0	0.0%	0.0000	0	0.0%	0	0.0%	0.0000
Worry	0	0.0%	0	0.0%	0.0000	0	0.0%	0	0.0%	0.0000
Consequences of bleeding	0	0.0%	0	0.0%	0.0000	0	0.0%	0	0.0%	0.0000
Emotional impact	0	0.0%	0	0.0%	0.0000	0	0.0%	0	0.0%	0.0000
Treatment concerns	0	0.0%	0	0.0%	0.0000	0	0.0%	0	0.0%	0.0000

Haemo-QoL-A Responder Analysis - Participants with ≥15% deterioration in Haemo-QoL-A scores

Measures	Unadjusted					After IPTW				
	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	(%)	
Physical functioning	0	0.0%	0	0.0%	0.0000	0	0.0%	0	0.0%	0.0000
Role functioning	0	0.0%	0	0.0%	0.0000	0	0.0%	0	0.0%	0.0000
Worry	0	0.0%	0	0.0%	0.0000	0	0.0%	0	0.0%	0.0000
Consequences of bleeding	0	0.0%	0	0.0%	0.0000	0	0.0%	0	0.0%	0.0000
Emotional impact	0	0.0%	0	0.0%	0.0000	0	0.0%	0	0.0%	0.0000

Treatment concerns	0	0.0%	0	0.0%	0.0000	0	0.0%	0	0.0%	0.0000

Data source: DHR from the start of data collection accompanying the application to approximately 6 months prior to the date of the final report required by the G-BA resolution for AbD
Acronyms: Haemo-QoL-A: Hemophilia Quality of Life assessment; SoC: standard of care

Haemo-QoL-A Progression Curve of Responder Analysis - Participants with ≥15% deterioration in Haemo-QoL-A scores

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

Measures	Unadjusted					After IPTW				
	Roctavian Cohort N=		SoC Cohort N=		p-value (Roctavian vs. SoC)	Roctavian Cohort N=		SoC Cohort N=		p-value (Roctavian vs. SoC)
	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

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

Measures	Unadjusted			After IPTW		
	Roctavian Cohort	SoC Cohort		Roctavian Cohort	SoC Cohort	

	N=		N=		p-value (Roctavian vs. SoC)		N=		N=		p-value (Roctavian vs. SoC)
	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 the start of data collection accompanying the application to approximately 6 months prior to the date of the final report required by the G-BA resolution for AbD
Acronyms: BPI-sf: Brief Pain Inventory – short form; SoC: standard of care

BPI-sf Progression Curve of Responder Analysis - Participants with ≥15% deterioration in BPI-sf scores

Table 15 Safety Outcomes for Roctavian and SoC Cohorts

Measures	Unadjusted						After IPTW					
	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
Hemophilia-related death	0	0.0%	0	0.0%	0.0000	0.00	0	0.0%	0	0.0%	0.0000	0.00
AEs leading to hospitalization – any cause	0	0.0%	0	0.0%	0.0000	0.00	0	0.0%	0	0.0%	0.0000	0.00
AEs leading to hospitalization – connected to hemophilia treatment	0	0.0%	0	0.0%	0.0000	0.00	0	0.0%	0	0.0%	0.0000	0.00
AEs leading to death – any cause	0	0.0%	0	0.0%	0.0000	0.00	0	0.0%	0	0.0%	0.0000	0.00
AEs leading to death – connected to hemophilia treatment	0	0.0%	0	0.0%	0.0000	0.00	0	0.0%	0	0.0%	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
Thromboembolic events – any cause	0	0.0%	0	0.0%	0.0000	0.00	0	0.0%	0	0.0%	0.0000	0.00
Thromboembolic events – connected to hemophilia treatment	0	0.0%	0	0.0%	0.0000	0.00	0	0.0%	0	0.0%	0.0000	0.00
Malignant neoplasms	0	0.0%	0	0.0%	0.0000	0.00	0	0.0%	0	0.0%	0.0000	0.00
Severe liver disease – any cause	0	0.0%	0	0.0%	0.0000	0.00	0	0.0%	0	0.0%	0.0000	0.00
Severe liver disease – connected to hemophilia treatment	0	0.0%	0	0.0%	0.0000	0.00	0	0.0%	0	0.0%	0.0000	0.00

Data source: DHR from the start of data collection accompanying the application to approximately 6 months prior to the date of the final report required by the G-BA resolution for AbD
Acronyms: SoC: standard of care; AE: adverse event; FVIII: coagulation factor VIII
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 16 Safety Outcomes for Roctavian and SoC Cohorts

Unadjusted Regression Model

Measures	Regression coefficient	95% Confidence Limits		r^2	p-value
		Lower Limit	Upper Limit		
All cause death	0.00	0.00	0.00	0.00	0.0000
Hemophilia-related death	0.00	0.00	0.00	0.00	0.0000
AEs leading to hospitalization – any cause	0.00	0.00	0.00	0.00	0.0000
AEs leading to hospitalization- connected to hemophilia treatment	0.00	0.00	0.00	0.00	0.0000
Development of FVIII inhibitors	0.00	0.00	0.00	0.00	0.0000
Thromboembolic events – any cause	0.00	0.00	0.00	0.00	0.0000
Thromboembolic events – connected to hemophilia treatment	0.00	0.00	0.00	0.00	0.0000
Malignant neoplasms	0.00	0.00	0.00	0.00	0.0000
Severe liver disease – any cause	0.00	0.00	0.00	0.00	0.0000
Severe liver disease – connected to hemophilia treatment	0.00	0.00	0.00	0.00	0.0000

IPTW-Adjusted Regression Model

Measures	Regression coefficient	95% Confidence Limits		r^2	p-value
		Lower Limit	Upper Limit		
All cause death	0.00	0.00	0.00	0.00	0.0000
Hemophilia-related death	0.00	0.00	0.00	0.00	0.0000
AEs leading to hospitalization – any cause	0.00	0.00	0.00	0.00	0.0000
AEs leading to hospitalization- connected to hemophilia treatment	0.00	0.00	0.00	0.00	0.0000
Development of FVIII inhibitors	0.00	0.00	0.00	0.00	0.0000
Thromboembolic events – any cause	0.00	0.00	0.00	0.00	0.0000
Thromboembolic events – connected to hemophilia treatment	0.00	0.00	0.00	0.00	0.0000
Malignant neoplasms	0.00	0.00	0.00	0.00	0.0000
Severe liver disease – any cause	0.00	0.00	0.00	0.00	0.0000
Severe liver disease – connected to hemophilia treatment	0.00	0.00	0.00	0.00	0.0000

Data source: DHR from the start of data collection accompanying the application to approximately 6 months prior to the date of the final report required by the G-BA resolution for AbD
Acronyms: AE: adverse event; FVIII: coagulation factor VIII
Note: Negative binomial regression models are used for events that can occur multiple times; Log binomial regression models are used for events that occur once.

Table 17 Free Text Safety Events for Roctavian and SoC Cohorts

Measures	Roctavian Cohort N=		SoC Cohort N=	
	N	(%)	N	(%)
Free Text Safety Event				
Safety event 1	0	0.0%	0	0.0%
Safety event 2	0	0.0%	0	0.0%
Safety event 3	0	0.0%	0	0.0%
Safety event 4	0	0.0%	0	0.0%

Data source: DHR from the start of data collection accompanying the application to approximately 6 months prior to the date of the final report required by the G-BA resolution for AbD
Acronyms: SoC: standard of care

Table 18 Time to Resumption of Prophylactic Treatment for Roctavian Cohort

Measures	Roctavian Cohort	
	N=	
	N	(%)
Participants 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	
Number of infusions/injections 3 months after resumption of prophylaxis		
SHL		
Mean	0.00	
SD	0.00	
Median	0	
Q1	0	
Q3	0	
Min	0	
Max	0	
EHL		
Mean	0.00	
SD	0.00	
Median	0	
Q1	0	

Q3	0		
Min	0		
Max	0		
Emicizumab			
Mean	0.00		
SD	0.00		
Median	0		
Q1	0		
Q3	0		
Min	0		
Max	0		
PD			
Mean	0.00		
SD	0.00		
Median	0		
Q1	0		
Q3	0		
Min	0		
Max	0		
Number of infusions/injections 6 months after resumption of prophylaxis			
SHL			
Mean	0.00		
SD	0.00		
Median	0		
Q1	0		
Q3	0		
Min	0		
Max	0		
EHL			
Mean	0.00		

SD	0.00		
Median	0		
Q1	0		
Q3	0		
Min	0		
Max	0		
Emicizumab			
Mean	0.00		
SD	0.00		
Median	0		
Q1	0		
Q3	0		
Min	0		
Max	0		
PD			
Mean	0.00		
SD	0.00		
Median	0		
Q1	0		
Q3	0		
Min	0		
Max	0		
Total FVIII dose 3 months after resumption of prophylaxis			
Mean	0.00		
SD	0.00		
Median	0		
Q1	0		
Q3	0		
Min	0		
Max	0		

Total FVIII dose 6 months after resumption of prophylaxis		
Mean	0.00	
SD	0.00	
Median	0	
Q1	0	
Q3	0	
Min	0	
Max	0	
Frequency of infusions/injections 3 months after resumption of prophylaxis		
2x per day	0	0.0%
Daily	0	0.0%
Every 2nd day	0	0.0%
Every 3rd day	0	0.0%
3x per week	0	0.0%
2x per week	0	0.0%
Weekly	0	0.0%
Every 10 days	0	0.0%
Every 2 weeks	0	0.0%
Monthly	0	0.0%
Frequency of infusions/injections 6 months after resumption of prophylaxis		
2x per day	0	0.0%
Daily	0	0.0%
Every 2nd day	0	0.0%
Every 3rd day	0	0.0%
3x per week	0	0.0%
2x per week	0	0.0%
Weekly	0	0.0%

Every 10 days	0	0.0%
Every 2 weeks	0	0.0%
Monthly	0	0.0%

Data source: DHR from the start of data collection accompanying the application to approximately 6 months prior to the date of the final report required by the G-BA resolution for AbD
Acronyms: SD: standard deviation; SHL: standard half-life; EHL: extended half-life; PD: plasma-derived

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

Haemo-QoL-A Scoring Manual

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:

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