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

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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>
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<tr><td></td><td>To compare the annualized bleeding rate for major, life threating, and joint bleeds.</td><td>• Major bleeding events.
• Life-threatening bleeding events.
• Bleeding events occurring in the joint.</td></tr>
<tr><td></td><td>To compare the proportion of 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></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

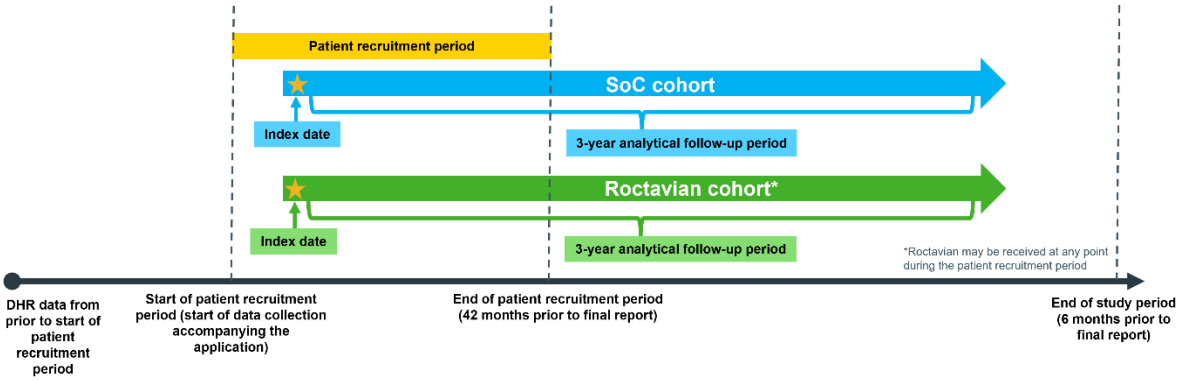
5. STUDY METHODS

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

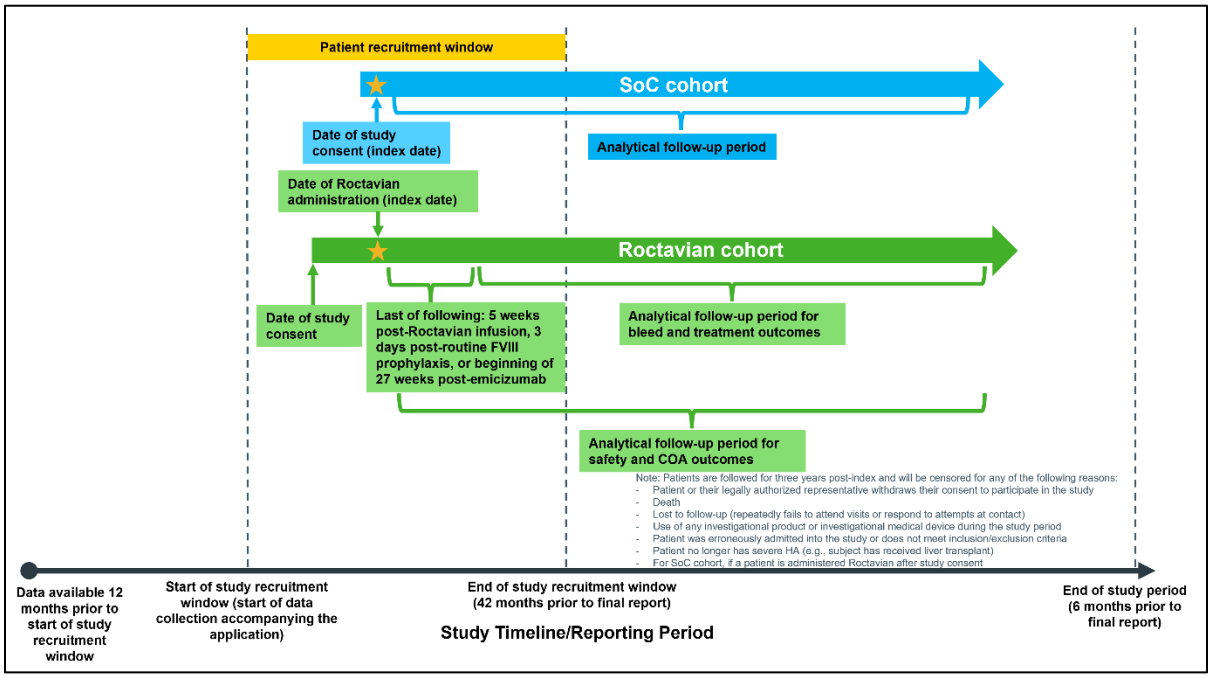


Figure note: Outcomes described from index through the end of the follow-up period for both the Roctavian Cohort and SoC Cohort. A participants' time in the analysis will only be censored in the event of a withdrawal, loss to follow-up, death or enrollment in an interventional trial (based on earliest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

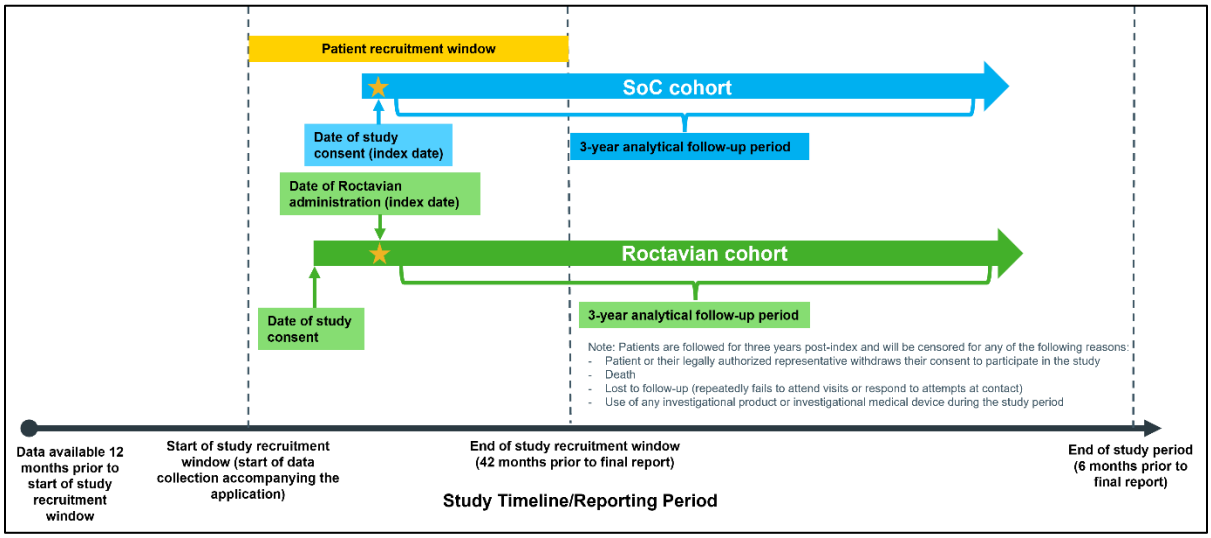


Figure note: For the Roctavian Cohort, analytical follow-up period for outcomes such as bleeding events and hemostatic therapy utilization will begin on 5 weeks post-infusion or 3 days after the end of routine FVIII prophylaxis (whichever occurs later), or 27 weeks after end of emicizumab prophylaxis 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

Appendix 2 – Selected Sections of Study 270-804 Including PS Score Development

1 INTRODUCTION

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 HA patients is largely governed by the level of residual FVIII expression. Severe HA is classified as FVIII activity less than 1% of wild-type (< 1 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 are frequent spontaneous bleeding episodes, predominantly in joints and soft tissues, with a substantially increased risk of death from hemorrhage when the brain is involved.

Clotting factor concentrates (CFCs) are the treatment of choice for people with hemophilia (both HA and hemophilia B) as they are safe and effective for treating and preventing bleeding events. There are two main types of CFCs: virally inactivated plasma-derived products made from plasma donated by human blood donors; and recombinant products manufactured using genetically engineered cells and recombinant technology, including standard half-life (SHL) and extended half-life (EHL) products (Srivastava, 2020). The development of non-factor replacement therapies such as emicizumab provides an alternative treatment approach; however, availability in clinical practice varies across geographies. Treatment guidelines recommend prophylaxis as the standard of care for individuals with severe HA (Srivastava, 2020).

Valoctocogene roxaparvovec (BMN 270) is an adeno-associated viral (AAV) 5-based gene therapy vector that expresses the SQ form of FVIII under the control of a hybrid human liver-specific promoter. BMN 270 is delivered by a single intravenous (IV) dose and is designed to achieve stable, durable expression of active FVIII in the plasma, synthesized from vector-transduced liver tissue.

The clinical efficacy and safety of valoctocogene roxaparvovec (BMN 270) are currently being evaluated in two clinical trials, a phase I/II single-arm, open-label, dose-escalation study 270-201 (BioMarin Pharmaceutical, 2022) and a pivotal Phase III single-arm, open-label study 270-301(BioMarin Pharmaceutical, 2021). Study 270-301 enrolled 112 participants after participating in a non-interventional study (NIS, 270-902) which prospectively followed participants in clinical practice whilst receiving prophylactic FVIII replacement with CFCs capturing information on bleeding events, medication use, and health-related quality of life (HRQL). There were also 22 subjects directly enrolled without participation in 270-902, utilizing a retrospective collection of bleeding events and medication use based on medical records and/or subject recall. Study 270-902 enrolled 294 subjects, with 225 having ≥6 months of follow-up at study end.

The primary efficacy endpoint for 270-301 was the change in the FVIII activity level during weeks 49-52 post-BMN 270 infusion from baseline, as measured by chromogenic substrate assay.

The secondary efficacy endpoints for 270-301 included:

- The change in the annualized utilization (IU/kg) of exogenous FVIII replacement therapy in the efficacy evaluation period (EEP) from baseline
    - The efficacy evaluation period was "week 5 to last visit" defined as 5 weeks post-infusion or 3 days after the end of routine FVIII prophylaxis through to the last visit by the data cutoff for the 1-year analysis
- The change in annualized bleeding rate (ABR) in the efficacy evaluation period ("week 5 to last visit" defined as 5 weeks post-infusion or 3 days after the end of routine FVIII prophylaxis through to the last visit by the data cutoff for the 1-year analysis) from baseline.

The inclusion of a prospective non-interventional study in the BMN 270 clinical trial program, i.e., 270-902, alongside the pivotal Phase III single-arm, open-label intra-individual study 270-301 provides the opportunity to undertake a comparison to an external control which will be of interest to the hemophilia community to confirm the primary trial results, as well as HTA assessors (i.e., early dialogue with G-BA [German reimbursement authority]).

This report details analyses comparing BMN 270 to prophylactic FVIII replacement using PS methodologies to account for bias in treatment allocation, and estimate the comparative effectiveness of BMN 270. In addition to methodology and results, scenario and sensitivity analyses are presented using alternative specifications of the propensity score, and alternative methods, to demonstrate the robustness of the results.

2 RESEARCH QUESTION AND OBJECTIVES

2.1 Research question/aim

To assess the comparative effectiveness of BMN 270 (observed in 270-301) to prophylactic-FVIII replacement (observed in 270-902) regarding ABR (treated and total) and proportion of subjects with zero bleeding events (treated and total) after adjusting for differences in observed baseline characteristics.

2.2 Primary objective

To compare BMN 270 treated subjects observed in 270-301 (i.e., the intervention cohort) to subjects treated with prophylactic-FVIII replacement observed in 270-902 (i.e., the control cohort) regarding:

i) Mean treated ABR

ii) Mean total ABR

iii) Proportion of subjects with zero bleeding events (treated bleeds)

iv) Proportion of subjects with zero bleeding events (total bleeds)

3 METHODS

3.1 Study design and dataset

This study is a retrospective comparative effectiveness assessment that utilized patient-level data (PLD) from BioMarin's ongoing 270 clinical trial program, including subjects administered BMN 270 in the 270-301 clinical trial (i.e., intervention cohort) and subjects who enrolled in the NIS 270-902 (i.e., control cohort).

Baseline characteristics from 270-301 and 270-902 were used to develop PSs to balance observable patient characteristics across the intervention and control cohorts to reduce confounding bias, as a consequence of a lack of randomization in treatment allocation. The PS-adjusted intervention and control cohorts are compared regarding outcomes of bleeding events, as measured by ABR and the proportion of subjects with zero bleeding events. Bleeding outcomes include comparisons of bleeding events that required FVIII-treatment (i.e., treated bleeds), as well as any recorded bleed (regardless of FVIII use, i.e., total bleeds). Bleeding outcomes are based on outcomes recorded in the respective trial datasets (see Section 3.1.1).

The primary analysis utilized standardized mortality ratio weighting (SMRW) to re-weight the baseline characteristics of the control cohort to more accurately reflect the intervention cohort (Brookhart, 2013; Desai and Franklin, 2019). SMRW is preferred to propensity score matching (PSM) and inverse probability treatment weighting (IPTW), as it creates more balanced intervention and control cohorts without re-weighting the intervention cohort, which increases interpretability of the analysis by ensuring consistency in reporting of sample size, baseline characteristics, and outcome data presented in the 270-301 clinical summary report (CSR). Furthermore, the use of weighting (rather than matching) ensures that the entire sample for the intervention cohort is used to inform the comparative effectiveness. This is likely to increase statistical power and is appropriate in the context of data collected within the confines of clinical trials (i.e., a relatively homogenous population with documented patient inclusion and exclusion criteria and treatment allocation).

Sensitivity analyses explore alternative PS adjustment methods and alternative baseline variables for the intervention cohort to inform PS development and the time horizon over which outcome data is captured. Scenario analyses explore the consistency of results from the primary analysis when utilizing data from alternative analysis populations and alternative methods for propensity scoring.

3.2 Propensity score development

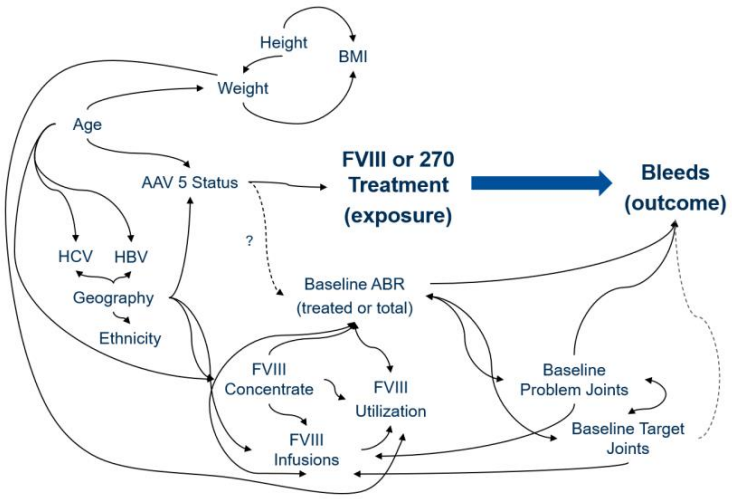
Propensity scoring is a method of balancing patients between studies using their observable characteristics. A propensity score is defined as the conditional probability of receiving treatment given an observed set of known covariates. These covariates can include both patient and disease characteristics but do not include outcome characteristics. Logistic regression of the exposure to the intervention given the observed set of known variables is then used to estimate the propensity score. Treatment is conditionally independent of the

covariates among patients with the same propensity score, allowing the replacement of covariates with a single summary value representing the probability of treatment assignment. Provided the propensity score includes all predictive patient characteristics, the comparisons created are unbiased.

This study considered all baseline demographics and baseline clinical characteristics consistently available across all studies, summarized in Section 3.3, for inclusion in the PS. A descriptive assessment (Figure 1) of the observed baseline covariates as potential confounders, and the relationship between treatment and the outcome of interest (e.g., univariate analyses) was undertaken to support decisions on the development of the PS.

In the descriptive assessment no 'true' confounders were identified due to the interventional nature of the data, the overall study design (i.e., 270-902 provided run-in data for 270-301 patients) and the similar inclusion/exclusion criteria between 270-902 and 270-301. The AAV status was the only variable associated with exposure and potentially associated with outcomes via baseline ABR. The key variables directly associated with outcomes are baseline ABR, problem joints and target joints. A visualization of potential associated between exposure and outcomes is presented in Figure 1.

Figure 1: Visualization of potential association between exposure and outcomes



Key: AAV, adeno-associated virus; ABR, annualized bleeding rate; BMI, body mass index; FVIII, factor VIII; HBV, hepatitis B virus; HCV, hepatitis C virus

In order to identify imbalances between groups, the Standardized Mean Difference (SMD) is presented for continuous 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 an imbalance between groups (Zhang, 2019). P-values are also presented, with a p-value of <0.1 generally recognized as an imbalance between groups (Peter C. Austin, 2011).

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

3.2.1 Standardized Mortality Ratio Weighting (SMRW)

The primary analysis aims to compare BMN 270 treated subjects observed in 270-301 (i.e., the intervention cohort) to subjects treated with prophylactic-FVIII replacement observed in 270-902 (i.e., the control cohort) regarding the mean treated and total ABR and the proportion of subjects with zero treated and total bleeding events.

In the base-case analysis, propensity scores are used to adjust the balance of baseline characteristics between the intervention and control cohorts via the implementation of SMRW. SMRW utilizes PS to reweight the control group (270-902) to match the characteristics of the intervention group (270-301). Consequently, this approach includes all subjects treated with BMN 270 in the analysis and uses all available data from the potential intervention and control cohorts. To weight the intervention group, the weight, W, assigned in the SMRW method for each individual *i*, based on the propensity score, P_i, is:

$W_i = 1$

For the control group, patients receive weights of:

$W_i = P_i / (1-P_i)$

The advantage of this approach is that multiple comparisons can be made (for instance with different subsets of the 270-902 study) without the results of the 270-301 study varying. Similarly, the results seen in the 270-301 cohort will match those seen with intra-patient comparisons, and within both the CSR and regulatory submissions. Were the 270-301 study reweighted, this would not be the case, and were matching used, some patients would be omitted.

3.3 Variables for inclusion

3.3.1 Baseline variables

Selection of variables for inclusion in the propensity score

Variables were included in propensity score based on either the statistical relationship with ABR based on regression analysis, or clinical relationship based on input from the study team and external clinical experts contributing to the study.

Application of regression analysis

In order to understand the variables which are statistically linked to bleeding outcomes (i.e., ABR) and therefore likely to bias any comparison, stepwise regression modeling was conducted. The candidate variables included in the regressions are summarized in Table 1.

Table 1: Summary of baseline variables for propensity score

Variable	Description	Time period	Measurement	Operational Notes
Baseline demographics and comorbid conditions*				
Age	Subject age in years	Baseline	Discrete	>18 years
Weight	Subject weight in kg	Baseline**	Continuous	00.00kg
Height	Subject height in meters (m)	Baseline**	Continuous	0.00m
Body Mass Index (BMI)	Subject BMI (>30 vs <30)	Baseline**	Continuous	BMI = weight/height^2 (kg/m^2)
Ethnicity	Subject ethnicity (Hispanic or Latino vs Not Hispanic or Latino)	Baseline	Categorical	Per study database records
HCV	Diagnosis of HCV (Y/N)	Baseline	Binary	
HBV	Diagnosis of HBV (Y/N)	Baseline	Binary	
Geographic location	Region subject resides	Baseline	Categorical	Per study database records
Baseline clinical characteristics				
No. of problem joints (PJs)	Number of PJs, as per the International Society of Thrombosis and Hemostasis (ISTH) definition, or three or more spontaneous bleeds into the same joint over 6 months (Blanchette, et al., 2014). (Y/N)	Baseline	Discrete	
Number of problem joints (PJs)	Number of PJs, which were identified by investigators at baseline and were defined as joints with any of the following symptoms: chronic joint pain, chronic synovitis, hemophilic arthropathy, limited motion, or recurrent bleeding. (Y/N)	Baseline	Discrete	
Baseline treated ABR	ABR of bleeding events treated with FVIII replacement (log-transformed)	Baseline	Continuous	Baseline treated ABR calculated based on bleeding events captured retrospectively 270-902 for the previous 26 weeks prior to enrolment. Calculated annualized metric of the number of bleeding events multiplied by 2.
Baseline FVIII utilization	Annual utilization of FVIII concentrates expressed as IU/kg/year	Baseline	Continuous	Baseline FVIII utilization calculated using data captured retrospectively in 270-902 for the previous 26 weeks prior to enrolment. Calculated annualized metric of the no. of IUs captured in this period multiplied by 2.
Baseline No. of FVIII infusions	Annual number of FVIII infusions expressed as No./year	Baseline	Continuous	Baseline annual no. of FVIII infusions calculated using data captured retrospectively in 270-902 for the previous 26 weeks prior to

Variable	Description	Time period	Measurement	Operational Notes
				enrolment. Calculate annualized metric of the number of FVIII infusions captured in this period multiplied by 2.
FVIII concentrate	Type of FVIII concentrate used at baseline: SHL EHL Both SHL and EHL Plasma-derived (PD) (EHL/Both vs SHL/PD)	Baseline	Categorical	International Nonproprietary Name (INN) used to group treatments as per description.

Note: *HIV not be described although some subjects in the 270-301 and 270-902 datasets had comorbid HIV, the populations utilized in the planned analyses exclude those patients with HIV.

**As weight and BMI are potentially relevant covariates for propensity score generation (FVIII prophylaxis is weight-based), measurements occurring outside of the baseline period during the follow-up period of 270-902 are considered to address missingness in these variables. Measurements outside of baseline were only utilized if data was missing at baseline.

Key: ABR, annualized bleeding rate; BMI, body mass index; EHL, extended half-life; FVIII, factor VIII; HBV, Hepatitis B virus; HCV, Hepatitis C virus; HIV, human immunodeficiency virus; INN, international non-proprietary name; ISTH, International Society of Thrombosis and Hemostasis; IU, international units; kg, kilograms; m, meters; PD, plasma-derived; PJ, problem joint; SHL, standard half-life; PJ, problem joint; Y/N, yes/no

The candidate variables were then used as explanatory variables in linear regression using both forwards and backward stepwise regression using the stepAIC function in R package MASS. The independent variable was log-transformed ABR for treated bleeds, observed in the prospective period of study 270-902. The variables reflect iterations of the regression model considering variables as binary, categorical, and continuous measures to ensure that variables potentially related to ABR were included (for example BMI was included as a dichotomized variable as BMI >= 30 vs BMI < 30). The full model regression analysis on post-baseline ABR in Study 270-902 residuals is summarized in Table 2.

Table 2: Full model regression analysis on post-baseline ABR in 270-902 residuals

Min	1Q	Median	3Q	Max
-1.94702	-0.61317	0.00769	0.58139	2.75456

Key: Q, quartile

The full model regression model of post-baseline ABR in 270-902 coefficients is presented in Table 3. The residual standard error was 0.8556 on 170 degrees of freedom. The multiple R-squared was 0.3655 and the adjusted R-squared was 0.3133. The F-statistics were 6.996 on 14 degrees of freedom (DF) and 170 DF, and the p-value was <0.001.

Table 3: Full model regression analysis on post-baseline ABR in 270-902 coefficients

	Estimate	SE	t-value	p-value
Intercept	1.128	0.360	3.139	0.002 **
Age	-0.009	0.008	-1.140	0.256
Obese: yes	-0.294	0.179	-1.644	0.102
log(mean ABR) of treated bleeds	0.524	0.066	7.985	<0.001 ***
Number of problem joints >0	-0.305	0.157	-1.937	0.054 .
History of exposure to Hepatitis B	-0.047	0.197	-0.237	0.8128
History of exposure to Hepatitis C	0.260	0.199	1.310	0.192
Prior FVIII replacement therapy: EHL	-0.376	0.168	-2.235	0.027 *
Baseline annualized FVIII infusion rate	-0.001	0.002	-0.544	0.587
Baseline annualized FVIII utilization	0.000	0.000	1.060	0.291
Region: East Asia	-0.400	0.241	-1.658	0.099 .
Region: Australia	0.090	0.223	0.403	0.688
Region: Africa	-0.329	0.226	-1.457	0.147
Region: South America	-0.439	0.224	-1.958	0.052 .
Region: North America	-0.052	0.234	-0.223	0.824

Notes: Significance codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

Key: SE, standard error

The backward stepwise selection based on AIC regression residuals is summarized in Table 4.

Table 4: Stepwise backward regression residuals

Min	1Q	Median	3Q	Max
-1.93981	-0.67403	-0.00085	0.62113	2.66439

Key: Q, quartile

The backward stepwise regression model is presented in Table 5. The residual standard error was 0.8465 on 177 DF. The multiple R-squared was 0.3534 and the adjusted R-squared was 0.3278. The F-statistic was 13.82 on 7 DF and 177 DF, and the p-value was <0.001.

Table 5: Stepwise backward regression coefficients

	Estimate	SE	t-value	p-value
Intercept	1.012	0.138	7.352	<0.001 ***
Obese: yes	-0.338	0.169	-1.992	0.048 *
log(mean ABR) of treated bleeds	0.522	0.063	8.271	<0.001 ***
Number of target joints >0	-0.306	0.153	-1.997	0.047 *
Prior FVIII replacement therapy: EHL	-0.311	0.152	-2.041	0.043 *
Region: East Asia	-0.403	0.225	-1.792	0.075 .
Region: Africa	-0.411	0.209	-1.967	0.051 .
Region: South America	-0.518	0.193	-2.682	0.008 **

Notes: Significance codes: 0 ‘***’ 0.001 ‘**’ 0.01 ‘*’ 0.05 ‘.’ 0.1 ‘ ‘ 1

Key: SE, standard error

The forward stepwise selection based on AIC regression residuals is summarized in Table 6.

Table 6: Stepwise forward regression residuals

Min	1Q	Median	3Q	Max
-1.93981	-0.67540	-0.00085	0.62113	2.66439

Key: Q, quartile

The forward stepwise regression model is presented in Table 7. The residual standard error was 0.8465 on 177 DF. The multiple R-squared was 0.3534 and the adjusted R-squared was 0.3278. The F-statistic was 13.82 on 7 DF and 177 DF, and the p-value was <0.001.

Table 7: Stepwise forward regression coefficients

	Estimate	SE	t-value	p-value
Intercept	1.012	0.1376	7.352	<0.001 ***
Obese: yes	-0.338	0.16941	-1.992	0.048 *
log(mean ABR) of treated bleeds	0.522	0.06311	8.271	<0.001 ***
Number of problem joints >0	-0.306	0.15301	-1.997	0.047 *
Prior FVIII replacement therapy: EHL	-0.311	0.1523	-2.041	0.043 *
Region: East Asia	-0.403	0.22478	-1.792	0.075 .
Region: Africa	-0.411	0.20872	-1.967	0.051 .
Region: South America	-0.518	0.19296	-2.682	0.008 **

Notes: Significance codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

Key: SE, standard error

Clinical input

Following the completion of the regression analysis, information about the statistical relationship with bleeding was provided to an expert panel including internal clinical experts, as well as, external study advisors. A summary of those consulted is presented in Table 8.

Table 8: Summary of clinical experts and study advisors

External study advisors	Internal clinical experts
Prof. Herve Chambost	Vanessa Newman
Prof. Johannes Oldenburg	Tara Robinson
Prof. Margareth Ozelo	Wing Yen Wong

A kick-off meeting was conducted with the study team and external advisors to consider the baseline variables considered to inform the PS (Table 1). Outputs from the stepwise regression analysis were also shared, and baseline variables that were not selected by the forward and backward stepwise models were discussed and considered for inclusion in the PS.

It was discussed that though weight and height measurements were missing at baseline, measurements were available for all but two subjects from the 270-902 prospective period. Weight and BMI were not selected when included in the stepwise selection. BMI was selected when dichotomized as obese vs. not.

Though region overall was selected in the stepwise selection, subsequent iteration (where regions were entered separated) identified that Asia, South America and Africa were the specific regions associated with bleeds.

Standard mean differences for baseline characteristics post-PS adjustment were generally smaller when baseline ABR was treated as a log-transformed continuous variable than a categorical variable. Continuous ABR in the original scale has a long-tail distribution,

therefore, log-transformation was preferred. There was good overlap in the distribution of propensity scores between the intervention and control groups for both variations of the PS.

Table 9 details the final list of variables included in the PS and the rationale for inclusion from this meeting.

Table 9: Baseline variables included in the propensity score (PS)

Variable	Definition	Agreement?			Note(s)
		Prof. Chambost	Prof. Oldenburg*	Prof. Ozelo	
Age	Continuous	Y	Y	Y	
Body Mass Index (BMI)	<30 vs. ≥30	Y	Y	Y	The justification for BMI (as opposed to weight) is explained further above
Region	East Asia (Y/N), Africa (Y/N), South America (Y/N)	Y	Y	Y	
No. of problem joints (PJs)	Y/N	Y	Y	Y	
Baseline treated ABR	Continuous (log-transformed)	Y	Y	Y	
Baseline FVIII utilization	Continuous	Y	Y	Y	
FVIII concentrate	SHL vs. EHL • 'pdFVIII' included in SHL • 'both SHL and EHL' included in EHL	Y	Y	Y	*"both SHL and EHL"* includes subjects utilizing both EHL and SHL during the time period

Notes: *Prof. Oldenburg's input was attained at a follow-up meeting

Key: BMI, body mass index; EHL, extended half-life; FVIII, factor VIII; N, no; pdFVIII, plasma-derived factor FVIII; PJ, problem joint; PS, propensity score; SHL, standard half-life; Y, y

Appendix 3:

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

Literature Review Summary

Date: January 24, 2024, Version 2.0

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List of Abbreviations

Abbreviation	Definition
ABR	Annualized bleeding rate
BMI	Body mass index
DHR	Deutsches Hämophilieregister
EHL	Extended half-life
FVIII	Coagulation factor VIII
HA	Hemophilia A
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
HTC	Hemophilia treatment center
KOL	Key opinion leader
MAIC	Matching-adjusted-indirect-comparison
PD	Plasma-derived
PDC	Proportion of days covered
PICOS	Population, Intervention, Control, Outcome, and Study Design
PK	Pharmacokinetic
PSM	Propensity score matching
PwSHA	People with severe hemophilia A
SAP	Statistical analysis plan
SHL	Standard half-life
US	United States

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1. Research Question and Purpose

This comprehensive literature review aimed to identify the risk factors or covariates associated with bleeding events among patients with severe hemophilia A (PwSHA). The findings from this review serve as a guideline for determining variables to be incorporated into the propensity score model for the Roctavian 270-603 study.

2. Literature Review Methods

2.1. Search Strategy

A comprehensive literature review was conducted to capture the most relevant and high-quality studies for addressing the research question. A fit-for-purpose search strategy was developed using key words, MeSH terms, and Boolean operators necessary to capture all relevant published literature. 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 **Table 1** for details), the search was executed on November 21, 2023, across the following online databases: Embase, OVID Medline, and the Cochrane Library (CDSR/CENTRAL).

Table 1: Search Strategy

#	Searches	Results	Annotations
1	pwsha.ab,ti. or ((severe* or severity).ab,ti. and (haemophilia-a or hemophilia-a).ti,ab.) or (exp *hemophilia a/ and (severe* or severity).ab,ti.)	16,680	population - title/abstract/ MeSH/Emtree
2	exp "blood clotting factor 8"/ or exp Factor VIII/ or (factor-8 or factor-viii or hemlibra or emicizumab or fviii* or f-viii* or rFVIII*).ab,ti. or exp emicizumab/ or exp "recombinant blood clotting factor 8"/ or (helixate$ or iblias$3 or kogenate$ or kovaltry$3 or advate$3 or immunate$3 or optivate$3 or haemoctin$3 or beriate$3 or haemate p$3 or octanate$3 or octanate lv$3 or wilate$3 or recombinate$3 or factane$3 or emoclot$3 or fanhdi$3 or wilnativ$3 or octafil$3 or amofil$3 or humaclot$3 or talate$3 or alphanate$3 or emowil$3 or klott$3 or aafact$3 or bioclate$3 or biostate$3 or wilate$3 or fibrogammin$ or voncento$ or recombinate$3).ti,ab. or (factor-replacement.ab,ti. not (factor-9 or factor-ix).ti,ab.)	79,883	intervention - title/abstract/ MeSH/Emtree
3	exp bleeding prophylaxis/ or exp prophylaxis/ or (prophylaxis or prophylactic* or prevention or preventative).ab,ti. or exp Premedication/ or exp *Hemorrhage/pc	3,210, 485	intervention - title/abstract/ MeSH/Emtree
4	exp valoctocogene roxaparvovec/ or (bmn-270 or bmn270 or valrox or roctavian or Valoctocogene).ab,ti.	202	intervention - title/abstract/ MeSH/Emtree
5	1 and ((2 and 3) or 4)	4,975	population + prophylactic rFVIII or roctavian
6	5 and ((Randomized Controlled Trial or Controlled Clinical Trial or Pragmatic Clinical Trial or Clinical Study or Adaptive Clinical	3,064	search narrowed to clinical trials -

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#	Searches	Results	Annotations
	Trial or Equivalence Trial or (Clinical Trial or Clinical Trial, Phase I or Clinical Trial, Phase II or Clinical Trial, Phase III or Clinical Trial, Phase IV or Clinical Trial Protocol) or Multicenter Study).pt. or Clinical Studies as Topic/ or exp Clinical Trial/ or exp Clinical Trials as Topic/ or Clinical Trial Protocol/ or Clinical Trial Protocols as Topic/ or exp "Clinical Trial (topic)"/ or Multicenter Study/ or Multicenter Studies as Topic/ or "Multicenter Study (topic)"/ or Randomization/ or Random Allocation/ or Double-Blind Method/ or Double Blind Procedure/ or Double-Blind Studies/ or Single-Blind Method/ or Single Blind Procedure/ or Single-Blind Studies/ or Placebos/ or Placebo/ or Control Groups/ or Control Group/ or Cross-Over Studies/ or Crossover Procedure/ or (random* or sham or placebo*).ti,ab,hw,kf. or ((singl* or doubl*) adj (blind* or dumm* or mask*)).ti,ab,hw,kf. or ((tripl* or trebl*) adj (blind* or dumm* or mask*)).ti,ab,hw,kf. or (control* adj3 (study or studies or trial* or group*)).ti,ab,hw,kf. or (clinical adj3 (study or studies or trial*)).ti,ab,hw,kf. or (Nonrandom* or non random* or non-random* or quasi-random* or quasirandom*).ti,ab,hw,kf. or (phase adj3 (study or studies or trial*)).ti,ab,hw,kf. or ((crossover or cross-over) adj3 (study or studies or trial*)).ti,ab,hw,kf. or ((multicent* or multi-cent*) adj3 (study or studies or trial*)).ti,ab,hw,kf. or allocated.ti,ab,hw. or ((open label or open-label) adj5 (study or studies or trial*)).ti,ab,hw,kf. or ((equivalence or superiority or non-inferiority or noninferiority) adj3 (study or studies or trial*)).ti,ab,hw,kf. or (pragmatic study or pragmatic studies).ti,ab,hw,kf. or ((pragmatic or practical) adj3 trial*).ti,ab,hw,kf. or ((quasiexperimental or quasi-experimental) adj3 (study or studies or trial*)).ti,ab,hw,kf. or trial.ti,kf.)		title/abstract/ MeSH/Emtree
7	5 and ((Observational or Retrospective or Registry or registries or "electronic medical record*" or database or emr or ehr or "claims data" or "administrative data" or "administrative claims" or "real world" or rwe or rwd).ab,ti,hw,sh,xs. or ("factual database" or "databases, factual").hw,sh,xs. or (Prospective or retrospective or cross-sectional or surveillance).ab,ti,sh,xs,pt. or exp epidemiologic studies/ or exp case control study/ or exp observational study/ or exp longitudinal study/ or exp postmarketing surveillance/ or exp prospective study/ or exp retrospective study/ or ('population based' or 'claims review' or 'claims analysis' or post-marketing or postmarketing or "phase Iv" or "phase 4" or cohort-study).ab,ti,sh,xs.)	2,205	search narrowed to observational/ RWE - title/ abstract/ MeSH/ Emtree
8	6 or 7	3,758	search narrowed to either study design
9	(8 and (adult or adults).ab,ti,xs,sh.) not (children or child or pediatrics).xs,sh,hw.	1,313	adult population
10	limit 8 to "all adult (19 plus years)" [Limit not valid in CCTR,CDSR,Embase; records were retained]	3,384	adult population
11	9 or (10 not (children or child or pediatrics).xs,sh,hw.)	2,016	search narrowed to adult population
12	11 not (animal/ or animals/ or (mice or mouse or mus or rat or rats or dogs or dog or monkey or cat).ab,ti. or (case-report* or preclinical or pre-clinical or invitro or in-vitro).ti,hw,pt.)	1,761	case reports/ preclinical literature excluded
13	remove duplicates from 12	1,537	deduped

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#	Searches	Results	Annotations
14	13 not (meeting or conference).pt.	567	Meeting abstracts excluded

2.2. Study Selection

Utilizing the Population, Intervention, Control, Outcome, and Study Design (PICOS) framework, fit-for-purpose study selection criteria was developed. The associated PICOS criteria are outlined in **Table 2**. Study selection was conducted in two phases, title/abstract screening, and full-text screening. The initial title and abstract screening were 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 hemophilia A treatment and bleeding events while considering covariates, either as part of the study design pre-randomization stratification or matching, or adjustments in the analysis, were included.

Table 2: PICOS Criteria for Risk Factors/Covariates Associated with Bleeding Events in PwSHA

PICOS Criteria	Description
Population	PwSHA without inhibitors, and 18+ years of age[a]
Intervention	Roctavian, FVIII prophylaxis, emicizumab prophylaxis
Control	Not specified
Outcome	Bleeding events
Study design	Clinical trial, intervention, or non-intervention real-world study (i.e., observational studies encompassing cohort, case control, and cross-sectional designs) Review articles lacking a pooled analysis Case series and were excluded.

[a] Mixed-age and inhibitor populations were included.

Abbreviations: FVIII: coagulation factor VIII; PwSHA: patients with severe hemophilia

2.3. Data Extraction

A data extraction form was created, and pilot tested including information on study characteristics, patient characteristics/study population, analysis details, and a covariate checklist. The covariate checklist allowed reviewers to indicate the presence or absence of specific covariates of interest based on covariates proposed for the propensity score found in the Statistical Analysis Plan (SAP) and other importance covariates based on input from the Key Opinion Leader (KOL). Once the data extraction form was piloted 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 **Table 3** for data extraction fields.

Table 3: Data Extraction Form Fields

Categories	Fields
Study characteristics	First author's name, year of publication, study location(s), study period, data source(s), study design, study design covariate components (i.e., pre-randomization stratification, matching), and the corresponding covariates used.
Patient characteristics/ Study population	Sample size, overall sample characteristics, reported age metrics (i.e., mean, range), hemophilia A severity, treatment exposures, interventions, and/or controls.

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Categories	Fields
Analysis details	List of bleeding outcomes, list of other outcomes, type of statistical analysis for bleeding outcomes, type of inferential statistics used (if applicable), and whether the inferential analysis was adjusted or stratified.
Covariate checklist	Age, weight/BMI, comorbidities, HTC/site/region/country, target joints, baseline prophylaxis class (SHL, EHL, PD, emicizumab), prophylaxis class switching (e.g., SHL/PD to EHL/emicizumab), baseline FVIII utilization, baseline/prior bleeding history (e.g., ABR), and lifestyle factors (e.g., physical activity).

Abbreviations: ABR: Annualized bleeding rate; BMI: body mass index; EHL: extended half-life; FVIII: coagulation factor VIII; HTC: hemophilia treatment center; PD: plasma-derived; SHL: standard half-life

2.4. Qualitative Synthesis

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 propensity score models for the Roctavian comparative effectiveness study in Germany.

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3. Literature Review Results

The comprehensive search ascertained 567 citations, which were all screened at the title/abstract phase. Of those, 121 articles were then assessed for eligibility to meet the PICOS criteria and ultimately, 16 publications[1-16] met criteria coming from 14 unique studies[1-12,15,16] (**Figure 1**).

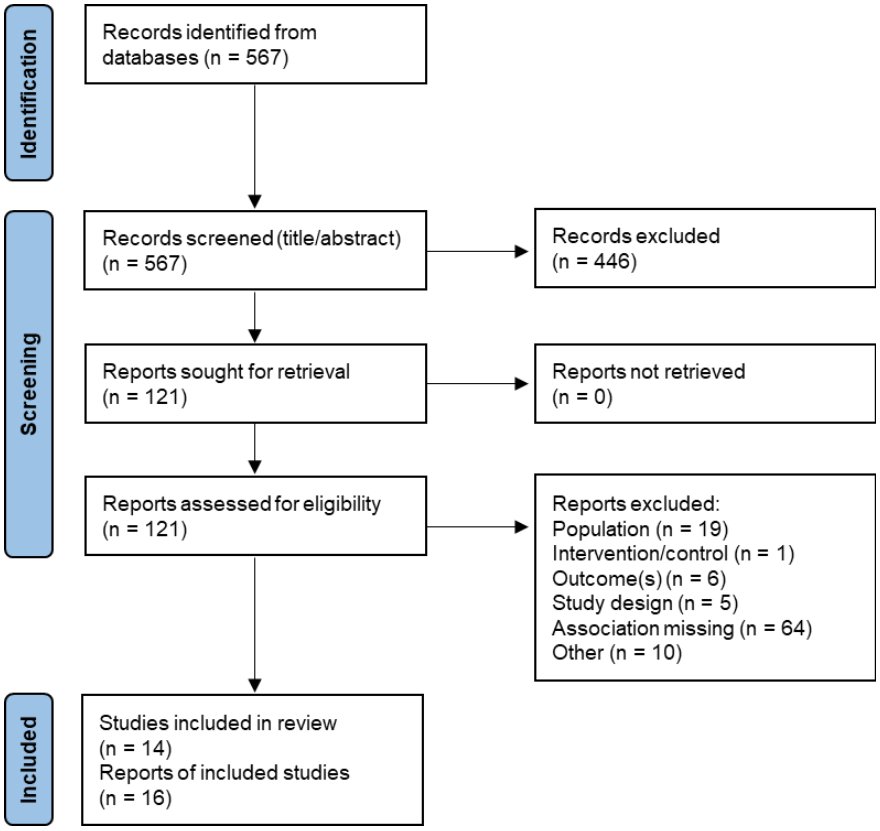


Figure 1: PRISMA Flow Diagram

Among the 14 included studies, 10 studies had data at least some data (e.g., one site) that originated in Germany. Regarding study design of the included studies, there were four clinical trials, three matching-adjusted-indirect-comparison (MAIC) studies, two prospective non-interventional studies, two retrospective cohort studies, two cross-sectional studies, and one pooled analysis of three clinical trials. Notable, only three studies focused exclusively on an adult patient population (≥ 18 years or older), while majority of the studies encompassed a mixed-age demographic. In addition, among the 14 studies, four studies included patients with different hemophilia severities.

Table 4 includes details regarding the covariate checklist. Age was the most common covariate, being documented in 11 studies. Weight or BMI was reported in six studies, target joints in five studies, and baseline or prior bleeding history (e.g., ABR) in four studies. Comorbidities (cancer, hepatitis B and C, human immunodeficiency virus (HIV) positivity, hypertension, liver failure, arthropathy or hemophilia arthropathy (appeared in two studies), synovitis, and osteoporosis), HTC, and baseline prophylaxis

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class (SHL, EHL, PD, emicizumab) were reported in three studies. Baseline FVIII utilization was reported in one study. Notably, prophylaxis class switching (e.g., SHL/PD to EHL/emicizumab), lifestyle and physical activity were not reported in any of studies included. Further, the MAIC/pooled analysis studies did not use any unique inclusions in the covariate checklist that did not already appear in other included studies.

Additional covariates that the covariate checklist did not capture, but were included in the studies were ethnicity, treatment duration, von Willebrand factor antigen, concurrent medications (bypass agents, non-steroid anti-inflammatory drugs, tranexamic acid, and corticosteroid), proportion of days covered (PDC) to study treatment, hemophilia severity, pharmacokinetic (PK)-guided dosing use, treatment strategy, exposure time, and prophylaxis vs on-demand treatment. However, the ethnicity and von Willebrand factor antigen covariates were only captured in the MAIC/pooled analyses and are therefore, de-prioritized, given MAIC/pooled analyses choose covariates based on characteristics and data captured in the studies used for analysis.

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Table 4. Covariate Checklist by Included Studies

First Author, Year of Publication	Covariate Checklist									
	Age	Weight/BMI	Comorbidities*	HTC/Site/Region/ Country	Target Joints	Baseline Prophylaxis Class (SHL, EHL, PD, emicizumab)	Prophylaxis Class Switching (e.g., SHL/PD To EHL/emicizumab)	Baseline FVIII Utilization	Baseline/Prior Bleeding History (e.g., ABR)	Lifestyle Factors (e.g., physical activity)
Powell, 2012	Yes	No	No	No	Yes	No	No	No	No	No
Manco-Johnson, 2013	No	No	No	No	Yes	No	No	No	Yes	No
Romanová, 2023	Yes	No	No	No	No	No	No	No	No	No
Giangrande, 2017	No	No	No	No	No	No	No	No	No	No
Hsieh, 2022	Yes	No	Yes	No	No	No	No	No	Yes	No
Ferri Grazzi, 2022	Yes	Yes	No	Yes	Yes	Yes	No	No	No	No
Olivieri, 2022	Yes	Yes	No	Yes	No	No	No	Yes	No	No
Ay, 2020	Yes	Yes	Yes	No	No	No	No	No	No	No
Miesbach, 2020	Yes	No	No	No	No	No	No	No	No	No
Konkle, 2015	Yes	No	No	No	Yes	No	No	No	No	No
Bukkems, 2023**	No	Yes	Yes	Yes	No	No	No	No	Yes	No
Astermark, 2023**	Yes	Yes	No	No	No	Yes	No	No	Yes	No
Klamroth, 2021**	Yes	No	No	No	Yes	Yes	No	No	No	No
Pocoski, 2016**	Yes	Yes	No	No	No	No	No	No	No	No
Total (yes)	**11**	**6**	**3**	**3**	**5**	**3**	**0**	**1**	**4**	**0**

Abbreviations: ABR: Annualized bleeding rate; BMI: body mass index; EHL: extended half-life; FVIII: coagulation factor VIII; HTC: hemophilia treatment center; PD: plasma-derived; SHL: standard half-life

*The list of comorbidities included: cancer, hepatitis B and C, HIV positivity, hypertension, liver failure, arthropathy or hemophilia arthropathy (reported in two studies), synovitis, osteoporosis.

**MAICs and pooled analyses studies.

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