270-603: FINAL REPORT

Study 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	270-603: Comparative Effectiveness of Roctavian to Standard of Care
Study Phase	Phase IV
Report Date	8 June 2026
Product	ROCTAVIAN; Hemostatic prophylaxis treatments (FVIII replacement therapies or emicizumab)
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This study is reported according to the principles set out the STROBE Initiative. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. J Clin Epidemiol. 2008 Apr;61(4):344-9. PMID: 18313558 also available at https://www.strobe-statement.org

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1 ABSTRACT

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
Phase and Type of Study	Phase IV non-interventional prospective study, to compare the effectiveness of Roctavian to the Standard of Care (SoC) hemostatic prophylaxis therapies
Rationale and Background	This study was undertaken to fulfill the Federal Joint Committee (G-BA) requirement for Routine Data Collection and Evaluations (Anwendungsbegleitende Datenerhebung; AbD). Specifically, this study provided data on the comparative effectiveness of valoctocogene roxaparvovec (Roctavian®) to Standard of Care (SoC) hemostatic prophylaxis treatments among people with severe HA (PwSHA) without a history of (or current) exogenous coagulation factor VIII (FVIII) inhibitors. Safety was also described (and compared, if warranted) among these populations to understand potential differences.

Research Question and Objectives	The aim of this non-interventional study was to evaluate the overall effectiveness and safety of Roctavian compared to SoC hemostatic prophylaxis treatment for PwSHA.
	
	The study objectives compare Roctavian and SoC prophylaxis treatment with FVIII or emicizumab, unless otherwise noted.
	
	• **Primary objective:** To compare the annualized bleeding rate for treated bleeds.
	• **Secondary objectives:**
	  ○ To compare the annualized bleeding rate for major, life threatening, and joint bleeds.
	  ○ To compare the proportion of people with zero bleeds for treated, major, life threatening, and joint bleeds.
	  ○ To compare the use of hemostatic medications.
	  ○ To compare joint health, quality of life, and pain.
	  ○ To compare safety events of interest.
	  ○ To describe time to resumption of prophylactic treatment among persons administered Roctavian.
	
	For this report, comparisons were not conducted due to limited sample sizes in both the Roctavian and SoC cohorts. Outcomes were described within each cohort for the outcomes listed in the objectives above.

Study Design	Prospective non-interventional study
Setting	Germany; Data collection beginning August 30, 2024
Study Population	Adult PwSHA without a history of (or current) inhibitors to FVIII in Germany

Variables and Data Source(s)	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
	Data for the study was collected via the German Hemophilia Registry (i.e., Deutsches Hämophilieregister [DHR]).

Statistical Methods	As per the protocol, comparison of outcomes were planned between the Roctavian cohort and SoC cohort after propensity score adjustment for differences in baseline characteristics (e.g., demographic and clinical variables recorded in the DHR prior to the index date). Due to the small sample sizes, no comparative analyses were conducted. However, all outcomes were described for the Roctavian and SoC cohorts.
Results	Results are reported as of 07 September 2025 (date of most recent data cut with source-verified data prior to the study being terminated) and 13 participants (four Roctavian, nine SoC) were enrolled in the 270-603 study from study sites across Germany to this date. Subsequent to the data cut, an additional one Roctavian and 14 SoC participants were enrolled in the study (as of 31 March 2026). An updated data cut was not undertaken due to the study termination occurring at the end of the enrollment period and minimal additional persons enrolling in the Roctavian cohort (key intervention for analyses). The Roctavian participants who enrolled in the 270-603 study reflect all persons who have been treated with Roctavian in Germany since the start of the requirement for Routine Data Collection and Evaluations. All persons enrolled in the study have continued to be followed with no discontinuations from the study. Baseline characteristics, comorbidities, and hemophilia burden were broadly comparable between the cohorts: similar age distributions (mean age at enrollment in Roctavian cohort of 40.50 versus 43.67 years in the SoC cohort); similar body mass index (BMI) distributions (approximately 50% with normal BMI and 50% overweight/obese); no reported liver fibrosis or cirrhosis in either cohort; no reported target joints in either cohort; majority of participants utilizing FVIII prophylaxis prior to enrollment (100% among Roctavian, 77.8% among SoC); and no switching of prophylaxis class during the baseline period (12 months prior to enrollment). No participants in the Roctavian cohort and one

	participant in the SoC cohort reported bleeding events during the baseline period. The Roctavian cohort had been followed for an average of 165 days, while the SoC cohort had been followed for an average of 212 days by the time of the data cut. One Roctavian participant and three SoC participants reported bleeding events during follow-up. Descriptively, Roctavian recipients had a lower bleeding burden (mean annualized bleeding rate [ABR] 0.80 bleeds per year; one participant with two bleeds) relative to SoC participants (mean ABR 1.64 bleeds per year; eight bleeds across three participants), with parallel patterns for joint bleeds (mean joint ABR 0.40 in Roctavian versus 1.47 in SoC cohort). A higher proportion of participants in the Roctavian cohort had zero bleeds (75.0%) versus the SoC cohort (66.7%). All participants in the Roctavian cohort and eight participants (88.9%) in the SoC cohort had hemostatic medication use during the follow-up period. Baseline Hemophilia Quality of Life assessment (Haemo-QoL-A) was available for all participants with more limited data available for the six month follow-up timepoint as not all participants have been followed for six months at the time of the datacut. Data on joint health and pain had higher levels of missingness than the Haemo-QoL-A. No adverse events were reported during follow-up.
Discussion	Study recruitment, particularly enrollment of the Roctavian cohort, reflected uptake of Roctavian in Germany. As of the data cut, only four PwSHA had been administered Roctavian since the start of the AbD, with one additional person administer Roctavian by 31 March 2026. Uptake and enrollment in 270-603 was <10% of the sample size required per the sample size calculation conducted by the Institute for Quality and Efficiency in Health Care (IQWiG) and detailed in the study protocol, at the time of study closure. The limited uptake and small sample size constrains interpretability of the results and indicated that the study was futile in providing meaningful data on the comparative effectiveness of Roctavian to SoC hemostatic prophylaxis after the AbD specified recruitment period. The study sponsor decided to voluntarily withdraw Roctavian from the German market (effective date of May 29, 2026); therefore, the 270-603 study was terminated. The study protocol and the SAP were not updated and the 18 month report was not submitted as originally planned. On 02 April 2026 the G-BA decided that the post-marketing data collection for Roctavian was not being carried out. The restriction of prescribing authority was revoked. The sponsor submitted a final report to GBA in June 2026.

2 LIST OF ABBREVIATIONS AND DEFINITIONS

Abbreviation	Full Form
AAV	Adeno-associated virus
AAV5	Adeno-associated virus serotype 5
AbD	Routine Data Collection and Evaluations
ABR	Annualized bleeding rate
AIR	Annualized infusion/injection rate
BMI	Body mass index
BPI-SF	Brief Pain Inventory-Short Form
BW	Body weight
CEC	Central Ethics Committee
COA	Clinical outcome assessment
CTA	Contract trial agreement
DHR	Deutsches Hämophilieregister
EHL	Extended half-life
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
FPI	First patient in
FVIII	Factor VIII
G-BA	Federal Joint Committee
HA	Hemophilia A
Haemo-QoL-A	Hemophilia Quality of Life Assessment
HCV	Hepatitis C virus
hFVIII-SQ	Human coagulation factor VIII with 14 amino acid long (SQ) linker sequence
HJHS	Hemophilia Joint Health Score
HTC	Hemophilia Treatment Center
IU	International unit
ITT	Immune tolerance therapy
IQWiG	Institute for Quality and Efficiency in Health Care
kg	Kilogram
LEC	Local Ethics Committee
mg	Milligram
PD	Plasma-derived

Abbreviation	Full Form
PEG	Polyethylene glycol
PI	Primary investigator
PwHA	People with hemophilia A
PwSHA	People with severe hemophilia A
Q1	Quartile 1
Q3	Quartile 3
QC	Quality control
SAP	Statistical analysis plan
SD	Standard deviation
SDV	Source data verification
SHL	Standard half-life
SIV	Site initiation visit
SoC	Standard of care

3 INVESTIGATORS/RESPONSIBLE PARTIES

Role	Contact Details
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4 MILESTONES

Milestone	Date
Protocol submission to G-BA	18 October 2023
Protocol resubmission to G-BA	25 April 2024
Start of data collection	30 August 2024
First patient enrolled	09 January 2025
End of patient enrollment	02 March 2026
End of data collection	02 April 2026
Final report of study results	08 June 2026

5 PROTOCOL AMENDMENTS AND UPDATES

None.

6 RATIONALE AND BACKGROUND

6.1 Background

6.1.1 Severe Hemophilia A

Hemophilia A (HA) is an X-linked recessive bleeding disorder that affects approximately 1 in 5,000 males.[1,2] It is caused by mutations in the factor VIII (FVIII) gene that codes for FVIII protein, an essential cofactor in the coagulation pathway. 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.[3] Early use of prophylaxis is recommended following diagnosis of HA to maintain joint health and prevent joint destruction.[4] However, despite the use of prophylaxis many patients still experience joint bleeds which may lead to joint deterioration over time.[5] Furthermore, not all bleeds may be clinically evident, as there are indications of subclinical bleeds in patients receiving treatment for their hemophilia.[4] 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.[6]

6.1.2 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.[7]

6.2 Routine Data Collection and Evaluations for Valoctocogene Roxaparvovec

6.2.1 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.[7] The resolution was preceded by a G-BA resolution of 03 February 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.[8]

Along with the resolution mandating the AbD, 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.[9]

The study sponsor decided to voluntarily withdraw Roctavian from the German market (effective date of May 29, 2026); therefore, the 270-603 study was terminated. The study protocol and the SAP were not updated and the 18 month report was not submitted. On 02 April 2026 the G-BA decided that the post-marketing data collection for Roctavian was not being carried out.[10,11] The restriction of prescribing authority was revoked. The sponsor submitted a final report to GBA in June 2026. [12,13] The decision to withdraw Roctavian was unrelated to any concerns regarding quality safety or efficacy of the product.

6.2.2 Compared Therapies

6.2.2.1 Roctavian®

Valoctocogene roxaparvovec (Roctavian) at the time of the study was 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.[12] 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 was a gene therapy based on an adeno-associated virus (AAV) vector that acts as a gene delivery vehicle. The vector was 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).[13] After a single intravenous administration, the vectors introduced the transgenes into liver cells and episomes are formed in the nucleus. As a result, the cells began continuous production of FVIII. Hemostasis was thus restored in the treated patients.

6.2.2.2 Factor FVIII 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 three 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 three 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.[6]

The list of approved factor VIII products used in Germany for the prophylactic treatment of severe HA at the time of the study are included in the Appendices.

6.2.2.3 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).[14]

6.3 Rationale

This study was undertaken to fulfill the G-BA requirement for the AbD. Specifically, this study was planned to provide data on the comparative effectiveness of Roctavian to Standard of Care (SoC) hemostatic prophylaxis treatments among people with severe HA (PwSHA) without a history of (or current) FVIII inhibitors. Safety was also to be described (and compared, if warranted) among these populations to understand potential differences.

7 RESEARCH QUESTION AND OBJECTIVES

The aim of this non-interventional study was 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 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 (ABR) for treated bleeds.	• Bleeding events requiring treatment with exogenous FVIII
Secondary	
To compare the ABR for major, life threatening, 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 threatening, 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)

Objectives	Endpoints
To describe time to resumption of prophylactic treatment among persons administered Roctavian.	• Resumption of prophylactic hemostatic treatments

As of 07 September 2025 (date of most recent data cut with source-verified data prior to the study being terminated), both the Roctavian cohort and the SoC cohort had less than ten participants enrolled and all participants had <12 months of follow-up. As sample sizes were small, comparisons between the study cohorts would not be meaningful and comparisons were not pursued. Although comparisons were not conducted, all study outcomes were described to inform feasibility of the study and progress. Analytic development of propensity scores and the following calculations/analyses were not performed due to sample size restrictions (<10 patients in each cohort):

- Baseline comparison of Roctavian and SoC cohorts for propensity score development
    - ***Rationale***: comparisons between cohorts of <10 patients would be underpowered and not meaningful
- Development and application of propensity scores
    - ***Rationale***: propensity score modeling with <10 patients per cohort would not produce robust model estimates and modeling may be subject to non-convergence, extreme weights, and violations of model assumptions
- Comparisons of bleeding outcomes, use of hemostatic medications, joint health, quality of life, pain, and safety outcomes between propensity score-adjusted cohorts
    - ***Rationale***: due to the small sample sizes, <12 months of follow-up, and lack of propensity score adjustment, comparisons would not be meaningful
- Exploration of unmeasured confounding using E-value calculations
    - ***Rationale***: calculation of E-values requires input of the relative risk between the two cohorts and relative risk was not calculated as comparisons between cohorts were not performed

8 RESEARCH METHODS

8.1 Study Design

This non-interventional cohort study enrolled 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 were followed based on data prospectively entered into the DHR. All participants were expected to have previously enrolled in the DHR per local regulations. Study participants consented for their data that was collected in the DHR to be utilized for this study, consistent with the requirements of the AbD. Participants provided consent during a study recruitment period beginning 30 August 2024 and ending 02 March 2026. This study recruitment window was planned to allows for three years of follow-up for each participant in the DHR prior to the data cut required for the original AbD specified final.

Participants were assigned to either the Roctavian cohort or SoC cohort based on the treatment that was received during the recruitment period. All participants receiving Roctavian during the recruitment period were assigned to the Roctavian cohort. Participants receiving SoC hemostatic prophylaxis treatment only during the recruitment period were assigned to the SoC cohort. The index date was 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 were planned to be followed for three years after the index date (analytical follow-up period) based on data extracted from the DHR. The above assumptions describe the treatment policy estimand, outlined in **Figure 1**. The hypothetical estimand was also planned to be considered as an alternative analytical follow-up period for the Roctavian participants and their bleeding events and hemostatic therapy utilization. Specifically, follow-up time would 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. Participants in the Roctavian cohort were planned to be censored at the time of resumption of SoC prophylaxis (event not observed as of data cut, therefore censoring was not implemented in analyses). See **Figure 2** for details. Due to the small sample size, the hypothetical estimand was not used for this report. Only results under the treatment policy estimand were reported.

Figure 1: Study Schema, Treatment Policy Estimand

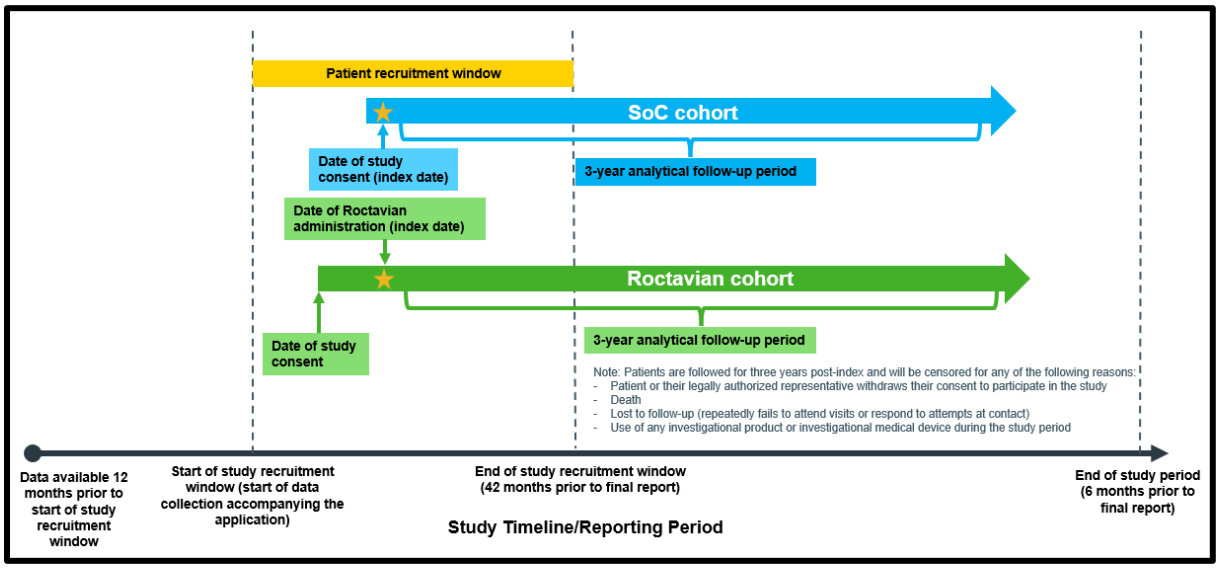
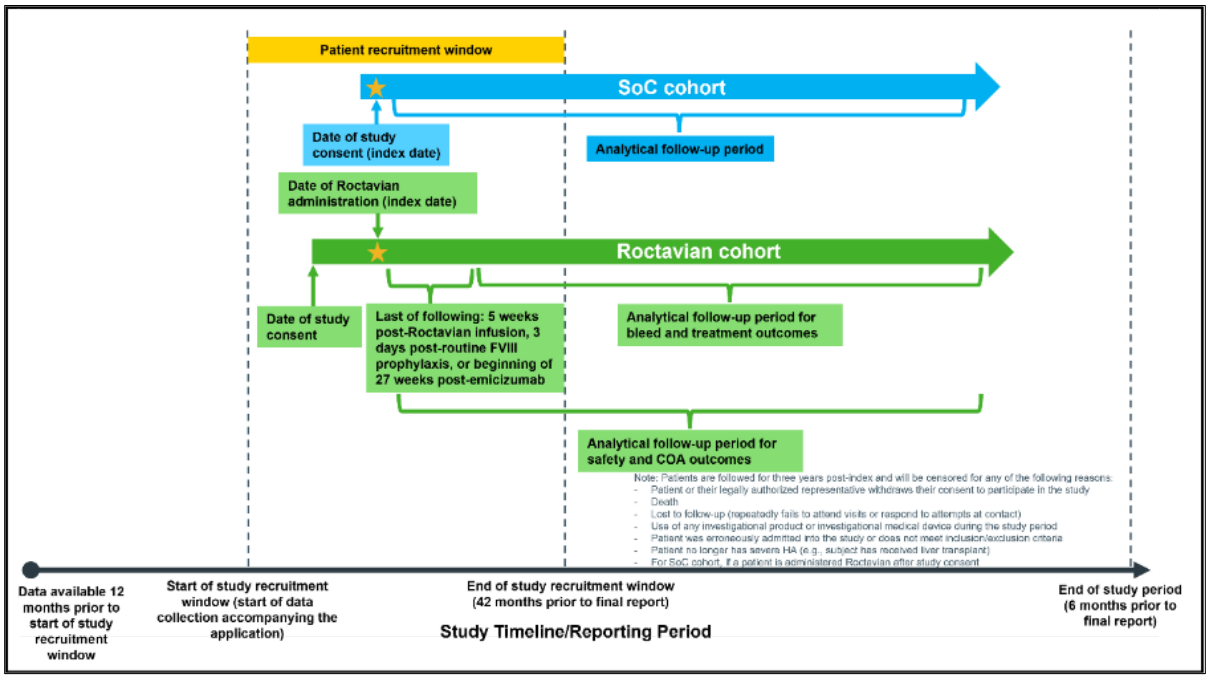


Figure 2: Study Schema, Hypothetical Estimand



Participants in the SoC cohort who subsequently received Roctavian during follow-up after the recruitment period were censored on the date of Roctavian infusion (event not observed in final data cut). If a participant consented to the AbD while on SoC and subsequently received Roctavian during the recruitment period, inclusion/exclusion were reassessed at the time of Roctavian administration. For these participants, baseline assessments, including patient reported outcome measures, were also reassessed at the time of Roctavian administration (event not observed as of data cut). If a participant in the SoC cohort subsequently received Roctavian during follow-up after the recruitment period, their data were censored for analysis (event not observed as of data cut). The study aimed to enroll at least 70 PwSHA into the Roctavian cohort and at least 330 PwSHA into the SoC cohort (per study protocol consistent with sample size calculations conducted by IQWiG). Data for the final report was extracted for any participants enrolled prior to 07 September 2025; this represented the most recent data cut with source-verified data, prior to the study being terminated.

Due to small sample sizes, the analysis for this report was strictly descriptive (rationale discussed in Section 7) . Baseline characteristics and events observed during the available follow-up period regarding bleeding events, use of hemostatic medication, clinical outcome assessments measuring joint health, quality of life, pain, and safety events were described for the Roctavian and SoC cohorts. PwSHA in Germany are generally seen at a Hemophilia Treatment Center (HTC) every 6 months and therefore it was expected that clinical outcome assessments of quality of life and pain were assessed at those timepoints, with joint health assessed at least annually. The occurrence of and time to resumption of prophylactic hemostatic therapy were also described among the Roctavian cohort during the follow-up period.

8.2 Setting

A total of eight study sites in Germany were identified, approached, and agreed to participate in the study. These centers were identified and selected based on the likelihood of administering gene therapy. All sites received ethics committee approval and were managed and monitored throughout the duration of the study according to the approved Clinical Operations Plan. Prior to enrolling participants, an on-site site initiation visit was performed at each site. Site participation and data quality were monitored through remote site management and subsequent on-site visits, which involved 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.

8.3 Study Population

Data for adult PwSHA without a history of (or current) inhibitors to FVIII in Germany who consent to the 270-603 study were extracted from the DHR. Study participants were treated with either Roctavian or SoC hemostatic prophylaxis treatments. The therapeutic treatment strategy for an individual who consented to this study was made independently of the decision to participate in the study and enrollment into this study did not inform the treatment strategy.

Study participants consented to have their individual clinical data recorded in the DHR consistent with the AbD and extracted for the purposes of this study. Eligibility criteria were confirmed by study investigators at the time of enrollment.

8.3.1 Inclusion Criteria

Individuals were eligible to be included in the study if all of the following criteria applied:

- Male PwSHA, as recorded in the DHR
- ≥18 years of age at index date
- Treatment with Roctavian or SoC hemostatic prophylaxis
    - Participant administered commercially available Roctavian

      OR
    - Received prophylactic treatment with exogenous FVIII or emicizumab
- Participant (or their legally authorized representative, if appropriate) provide written, signed informed consent for participation in the study

8.3.2 Exclusion Criteria

Individuals were excluded from the study if any of the following criteria applied:

- Were currently in, or previously participated (in the last 12 months before index) in, an interventional clinical trial involving an investigational product to treat HA at index
- History of inhibitors against FVIII ever (or current) as recorded in the DHR prior to index
- Presence of acute infections or uncontrolled chronic infections, and/or known significant hepatic fibrosis or cirrhosis at index

8.4 Variables

8.4.1 Exposure

Participants receiving Roctavian were enrolled in the Roctavian cohort. Participants in the SoC cohort may have received emicizumab, standard half-life (SHL) products, extended half-life (EHL) products, or plasma-derived (PD) products.

8.4.2 Outcomes

Outcomes were assessed across four domains: bleeding events, treatment utilization, clinical outcome assessments (COAs), and safety events. The primary endpoint was the annualized bleeding rate (ABR) for treated bleeds. Secondary bleeding outcomes included ABRs for major, life-threatening, and joint bleeds, as well as the proportion of participants with zero bleeds in each category.

Treatment-related outcomes focused on the use of hemostatic medications, including cumulative prophylactic and on-demand FVIII or emicizumab usage, infusion/injection rates, and time to resumption of prophylaxis among Roctavian-treated participants. COAs measured joint health (HJHS), Haemo-QoL-A), and pain (BPI-sf), were collected at baseline and during the follow-up.

Safety outcomes included all-cause and bleeding-related mortality, adverse events leading to hospitalization or death, and targeted events such as FVIII inhibitor development, thromboembolic events, malignant neoplasms, and severe liver disease.

8.4.3 Covariates

Patient baseline characteristics were described and informed the comparability of the Roctavian and SoC cohorts. Certain characteristics were planned to be utilized to develop the propensity score for future comparative analysis. These characteristics included participant age at consent, height, weight, body mass index (BMI), ABR, FVIII utilization, prophylaxis class switching, target joints, prior type of bleeds, HJHS, Haemo-QoL-A, BPI-sf, and comorbidities including hepatitis C virus (HCV), chronic liver disease, malignancy, hypertension, and osteoporosis.

8.5 Study Procedures

8.5.1 Data Source

The DHR is a disease registry maintained by the Paul-Ehrlich-Institute, in cooperation with the Gesellschaft für Thrombose- und Hämostaseforschung e. V., the Deutsche

Hämophiliegesellschaft zur Bekämpfung von Blutungskrankheiten e. V., and the Interessengemeinschaft Hämophiler e. V..

The DHR is a registry for medical research and quality assurance in the care of persons with the diseases HA, 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.[15]

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

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

Updates to the DHR data source have been implemented to incorporate all fields required for the study and quick response codes have been added and programmed for data collection of the COAs. SDV visits were scheduled to occur, four weeks post-first patient in (FPI) at each site to ensure consistent and accurate data entry. Clinical research associates were granted direct monitoring access to the DHR, with query processes in place to ensure accurate and complete data collection as per the study protocol.

8.5.2 Protection of Human Subjects

Measures were taken to ensure the privacy of subject data in accordance with the principals of the DHR. All applicable regulations and guidelines in the relevant locality, country, and/or region were followed to protect the privacy of subject data. The study was conducted in accordance with the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) Code of Conduct, the International Society for Pharmacoepidemiology Guidelines for Good Pharmacoepidemiology Practices, the Declaration of Helsinki and Council for International Organizations of Medical Sciences International Ethical Guidelines its amendments, and any applicable national guidelines, laws

and regulations. All participating entities and individuals acting on their behalf commit to adhere to the rules of the ENCePP Code of Conduct in their entirety.

8.6 Statistical Methods

8.6.1 Main Statistical Methods

All measures were reported descriptively for the Roctavian and SoC cohorts, including timelines up to six months to align with maximum length of follow-up at the time of the datacut. Only patients enrolled before the data cut date were included in the analysis.

8.6.2 Specific Analyses

8.6.2.1 Primary Objective

Annualized bleeding rates for treated bleeding events were described for the Roctavian and SoC cohorts. Participants with no bleeds were reported but data entered into the DHR had an ABR of zero (i.e., the data was not considered missing). ABRs were calculated for each participant as the number of bleeds divided by the time between the start of follow-up and censoring event, annualized to the number in 1 year. The mean, standard deviation (SD), median, quartile 1 (Q1), quartile 3 (Q3), minimum, and maximum for each cohort were reported.

8.6.2.2 Secondary Objectives

8.6.2.2.1 Annualized bleeding rate for major, life-threatening, and joint bleeds

ABRs for other bleeding outcomes (major bleeds, life-threatening bleeds, and joint bleeds) were also described for the Roctavian and SoC cohorts using mean, SD, median, Q1, Q3, minimum, and maximum.

8.6.2.2.2 Proportion of participants with zero bleeds

The proportion of participants with zero bleeding events (treated bleeds, major bleeds, life-threatening bleeds, and joint bleeds) during the follow-up period were reported for the Roctavian cohort and SoC cohort. As per the protocol, this analysis was planned to only include participants with follow-up for the full time over which the proportion was calculated (i.e., 1, 2, and 3 years), however, due to short follow-up time for participants at the data cut, all available follow-up time was used for analyses.

8.6.2.2.3 Use of hemostatic medications

Cumulative hemostatic medication use was reported for the Roctavian and SoC cohorts. The proportion of participants (n, %) with any hemostatic medication use was reported over all available follow-up, as well as measures of utilization (IU or milligrams [mg] per kilogram

[kg], annualized infusion/injection rate [AIR]) for prophylactic and on-demand use (mean, SD, median, Q1, Q3, minimum, and maximum).

8.6.2.2.4 Clinical outcome assessments

The HJHS, Haemo-QoL-A, and BPI-sf assessments were intended to be collected at participants index date (baseline measure), and at subsequent visits consistent with clinical practice and the study protocol (every 6 months for Haemo-QoL-A and BPI-sf and annually for HJHS). Descriptive statistics (mean, SD, median, Q1, Q3, minimum, maximum) were used to summarize COA scores at the baseline and subsequent visits (if available).

The HJHS measures joint health in the left and right knees, left and right ankles, left and right elbows, and global gait score. Scores range from 0 to 124 points. Scores within each of the six joint categories were summed.

The Haemo-QoL-A consists of 41 questions covering six domains (physical functioning, role functioning, worry, consequences of bleeding, emotional impact, and treatment concerns). Items were answered by participants on a 6-point Likert scale, ranging from 0 (none of the time) to 5 (all of the time). Higher scores indicated better health-related quality of life or less impairment for that particular measure.

The BPI-sf includes questions assessing pain intensity and pain interference. The pain intensity items use an 11-point numerical scale with zero signifying (“no pain”) and ten signifying (“pain as bad as you can imagine”). The pain interference scale assesses the degree to which pain interferes with seven 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 ten signifying “completely interferes.” Summary statistics for each question were calculated.

8.6.2.2.5 Safety events

Safety events for the Roctavian and SoC cohorts were described by frequency (n, %) within each cohort. In addition to the safety outcomes identified in Section 8.4.2, any additional free text safety events that were noted in the DHR were described.

8.6.2.2.6 Time to resumption of prophylactic treatment

For participants in the Roctavian cohort, time to resumption of prophylactic treatment, as well, as number and frequency of infusions after resumption of prophylaxis was reported for patients who resumed SoC prophylaxis after Roctavian administration during the follow-up

period using mean, SD, median, Q1, Q3, minimum, and maximum. Note that no events of resumption of prophylaxis occurred at the time of the data cut.

8.6.2.3 Subgroup Analyses

Due to the small cohort sizes and <12 months of follow-up for all participants, no subgroup analyses were conducted.

8.6.2.4 Sensitivity Analyses

Due to the small cohort sizes and <12 months of follow-up for all participants, no sensitivity analyses were conducted.

8.7 Quality Control

All aspects of the study were conducted within the framework of the IQVIA Quality Management System. A Quality Control (QC) checklist was used in producing the results and report. The IQVIA Advanced Analytics team employed a two-programmer approach to ensure accuracy and reproducibility of coding, including a multi-point QC checklist for retrospective database studies and independent double-programming of analyses.

9 RESULTS

9.1 Site Activation

A total of eight study sites in Germany were identified, approached, and agreed to participate in the study (**Table 2**, **Appendix 2 Table 5**). These centers were identified and selected based on the likelihood of administering gene therapy. Seven of the sites received Central Ethics Committee (CEC) approval, as well as Local Ethics Committee (LEC) approval where applicable; one site was still in the process for LEC submission after the enrollment period end date and study closure. The site with outstanding LEC submission was engaged after the initial outreach phase. Additionally, per the site's request, no LEC documents were completed and signed until the CTA was fully executed. As a result, LEC submission could only proceed once the CTA was finalized, and was pending signatures when the study was terminated. Relevant supervisory bodies (GKV, PKV, and KBV) were notified about the study start in parallel with the CEC and LEC submissions, per German regulatory study requirements.

Table 2: Study Sites, Current Status

Site	Activation Date	ATMP-QS-RL	FPI
Vivantes Klinikum im Friedrichshain	08 Jan 2025	Ready	09 Jan 2025
Universitätsklinikum Regensburg	Under CTA review; Expected activation TBC	In Prep	-
Universitaetsklinikum Hamburg-Eppendorf	19 Jan 2026	Ready	-
Universitaetsklinikum Frankfurt Goethe-Universitaet	01 Dec 2025	Ready	-
Universitaetsklinikum Bonn AoeR	08 Nov 2024 (Favorable LEC vote determined final site activation)	Ready	23 April 2025
Universitaetsklinikum Leipzig AoeR	26 Nov 2024	Ready	-
Medizinische Hochschule Hannover	14 Mar 2025	Ready	-
Klinikum der Universitaet Muenchen	CTA finalization TBC, LEC submission pending	In prep	-

Acronyms: AMTP-QS-RL: ATMP-Qualitätssicherungs-Richtlinie; CTA: contract trial agreement; FPI: first patient in; LEC: Local Ethics Committee; TBC: to be completed

Altogether, there were two study sites that were not activated at the time of study closure, with delays in part related to sites not having potential Roctavian patients to dose, as well as site specific limitations. The Universitätsklinikum Regensburg site had paused completing the first round of CTA review, due to site staffing shortages (pending resumption of CTA negotiations) and the Klinikum Der Universitaet Muenchen site had a partially executed CTA, with pending site initiation visit and LEC submissions. CTA progress was expected to be completed closer to the site identifying patients who may be dosed with Roctavian.

9.2 Study Population

There were four study participants in the Roctavian cohort and nine participants in the SoC cohort. All individuals who were administered Roctavian were prioritized for enrollment, while SoC enrollment was scaled to achieve a ratio of 1:3-5 participants, relative to the Roctavian cohort. Therefore, the analysis dataset included a total of 13 participants (**Appendix 2 Table 6**).

9.3 Baseline Characteristics

The baseline characteristics of the four Roctavian and nine SoC participants are reported in **Table 3** and **Appendix 2 Table 7**. Participant age at date of enrollment was similar in the Roctavian cohort (mean: 40.50 years, SD: 8.35; median: 42.5) to the SoC cohort (mean: 43.67 years, SD: 11.67; median: 41.0 years).

Regarding clinical characteristics at baseline for Roctavian and SoC cohorts, reported in **Appendix 2 Table 8**, approximately half of Roctavian and SoC participants had a normal BMI of 18.5-<25 (two (50.0%) in Roctavian and five (55.6%) in SoC). Only one (25.0%) Roctavian participant had an active and/or cured HCV infection, while all other participants had unknown or no infection indicated. In the Roctavian cohort, all four participants were receiving FVIII products for prophylactic treatment at baseline. Similarly, in the SoC cohort, seven (77.8%) participants had FVIII prophylaxis, one (11.1%) participant received FVIII and non-factor prophylaxis, and one (11.1%) participant had no information (note this participant had missing data but had evidence confirming inclusion into the study). No switches in prophylaxis classes were observed for Roctavian or SoC cohorts in the one year prior to study enrollment. In both cohorts, there was no presence of chronic liver disease (other than HCV noted above), other comorbidities of interest (malignancy, hypertension, and osteoporosis), nor target joints. Only Roctavian participants had an AAV5 antibody status and all four were AAV5 negative. No participants (from either cohort) had any immunosuppression therapy prior to enrollment. The mean annualized baseline FVIII utilization among four Roctavian participants and eight SoC participants with prophylaxis data entered was 7,611.04 (SD: 7,940.86) IU/kg/year and 4,126.59 (SD: 1,878.02)

IU/kg/year, respectively. It should be noted that treatment data collection appeared to not be complete for all participants, due to differences in reporting preferences for patients and healthcare providers. Activities to ensure more complete data collection were ongoing at the time of the study termination; though not complete at the time of this report. Only one bleed was reported in the SoC cohort and zero in the Roctavian cohort prior to study enrollment. As shown in **Table 3** below, baseline characteristics that would have been included in propensity score adjustment were largely similar between the Roctavian and SoC cohorts.

Table 3: Baseline Characteristics For Inclusion in Propensity Scores

Measures	Roctavian Cohort		SoC Cohort	
	N=4		N=9	
	N	(%)	N	(%)
Age (years)	4	100.0%	9	100.0%
Mean	40.50		43.67	
SD	8.35		11.67	
Median	42.5		41	
Height (cm)	4	100.0%	8	88.9%
Mean	189.75		178.63	
SD	7.85		5.64	
Median	193.5		179.5	
Weight (kg)	4	100.0%	8	88.9%
Mean	90.75		79.63	
SD	18.41		9.86	
Median	87		79.5	
BMI	4	100.0%	8	88.9%
<18.50	0	0.0%	0	0.0%
18.50 - <25.00	2	50.0%	5	55.6%
25.00 - <30.00	1	25.0%	3	33.3%
≥30.00	1	25.0%	0	0.0%
HCV infection				
No infection	1	25.0%	0	0.0%
Active and/or cured infection	1	25.0%	0	0.0%
Unknown	2	50.0%	9	100.0%

Measures	Roctavian Cohort		SoC Cohort	
	N=4		N=9	
	N	(%)	N	(%)
Chronic liver disease				
Liver fibrosis	0	0.0%	0	0.0%
Liver cirrhosis	0	0.0%	0	0.0%
Not specified/unknown	4	100.0%	9	100.0%
Other comorbidities				
Malignancy	0	0.0%	0	0.0%
Hypertension	0	0.0%	0	0.0%
Osteoporosis	0	0.0%	0	0.0%
Targeted joints				
Yes	0	0.0%	0	0.0%
No	4	100.0%	9	100.0%
Unknown	0	0.0%	0	0.0%
SoC switch				
No change	4	100.0%	8	88.9%
Change in 1 year prior to index	0	0.0%	0	0.0%
SHL to EHL	-	-	0	0.0%
SHL to emicizumab	-	-	0	0.0%
EHL to emicizumab	-	-	0	0.0%
Emicizumab to SHL	-	-	0	0.0%
Emicizumab to EHL	-	-	0	0.0%
Emicizumab to PD	-	-	0	0.0%
PD to emicizumab	-	-	0	0.0%
Annualized baseline FVIII utilization (IU/kg/year), prophylaxis	4	100.0%	8	88.9%
Mean	7,611.04	.	4,126.59	
SD	7,940.86	.	1,878.02	
Median	4,094.80	.	3,890.84	
Baseline ABR, overall				
Mean	0.00		1.40	
SD	0.00		4.20	

Measures	Roctavian Cohort		SoC Cohort	
	N=4		N=9	
	N	(%)	N	(%)
Median	0.00		0.00	

Acronyms: ABR: annualized bleeding rate; BMI: body mass index; EHL: extended half-life; FVIII: coagulation factor FVIII; HCV: hepatitis C virus; PD: plasma-derived; SD: standard deviation; SHL: standard half-life; SoC: standard of care.

Note: Baseline COA variables are not included in this table, but will be considered for future propensity score adjustment.

9.4 Main Results

The overall mean follow-up time for the Roctavian and SoC cohorts was 165.25 (SD: 87.88) days and 212.44 (SD: 20.26) days from enrollment up to 07 September 2025, respectively. In addition, two Roctavian participants and all nine SoC participants had at least six months of follow-up.

9.4.1 Primary Objective

Among four participants in the Roctavian cohort, only one participant had a bleed and experienced two treated bleeds, 147 and 190 days after Roctavian administration, resulting in a mean ABR of 0.80 (SD: 1.60) treated bleeds per year for the cohort. In the SoC cohort, three participants reported bleeds reported (1 individual with a single treated bleed and 2 individuals with 2-5 treated blees; a total of eight bleeds across the 3 individuals), resulting in a mean ABR of 1.64 (SD: 2.91) treated bleeds for the cohort. Treated ABR results are reported in **Table 4**, as well as **Appendix 2 Table 9** in the appendix. Note all available follow-up data through the datacut were used for these analyses, unless otherwise stated.

Table 4: Treated ABR for Roctavian and SoC Cohorts

Measures	Roctavian Cohort		SoC Cohort	
	N=4		N=9	
	N	(%)	N	(%)
Follow-up time (days) from enrollment to data cut*	4	100.0%	9	100.0%
Mean	165.25		212.44	
SD	87.88		20.26	
Median	183		206	
Q1	95.5		193	
Q3	235		235	
Min	53		193	

Measures	Roctavian Cohort		SoC Cohort	
	N=4		N=9	
	N	(%)	N	(%)
Max	242		235	
Number of participants with at least 6 months of follow-up from enrollment to data cut	2	50.0%	9	100.0%
Treated ABR				
Mean	0.80		1.64	
SD	1.60		2.91	
Median	0.00		0.00	
Q1	0.00		0.00	
Q3	1.60		1.55	
Min	0.00		0.00	
Max	3.20		7.57	
N of treated bleeding events	2		8	
N of participants with bleeding events				
1 bleeding event	0	0.0%	1	11.1%
2-5 bleeding events	1	25.0%	2	22.2%

Acronyms: ABR: annualized bleeding rate; SD: standard deviation; SoC: standard of care
*7 September 2025 was the data cut date for the final analysis.

9.4.2 Secondary Objectives

9.4.2.1 Major, Life-threatening, and Joint Bleeds

Among the treated bleeds reported in the primary objective, the one bleed for the Roctavian participant was a joint bleed and seven of the 8 bleeds in the SoC cohort were joint bleeds resulting in mean joint bleed ABRs of 0.40 (SD: 0.80) and 1.47 (SD: 2.96), respectively (**Appendix 2 Table 10)**. No major or life-threatening bleeds were reported in the data cut. Note all available follow-up data were used for these analyses.

9.4.2.2 Proportion of Zero Bleeds

The proportion of participants with zero bleeds (based on available follow-up) is shown in **Appendix 2 Table 11**. Seventy-five percent of Roctavian and 66.7% of SoC participants did not have a treated bleed, and 75.0% and 77.8% did not have a joint bleed, respectively.

9.4.2.3 Hemostatic Medication Use

Hemostatic medication use after study enrollment using the treatment policy estimand is shown in **Appendix 2 Table 12**. In the Roctavian cohort, all four participants had hemostatic

medication use, with one participant (25.0%) having hemostatic medication use for bleeds or short-term prophylaxis. The mean infusion/injection rate per year was 10.57 (SD: 7.87) and the mean AIR was 78.89 (SD: 29.31) infusions/injections per year. Among the four Roctavian participants, the mean total prophylactic FVIII utilization was 41,500.00 (SD: 25,592.97) IUs and the mean total prophylactic FVIII utilization per participant per kg was 456.45 (SD: 283.88) IUs/kg. No participants in the Roctavian cohort had non-factor utilization during the follow-up period.

In the SoC cohort, all eight participants with treatment data (1 participant did not have any treatment data reported) reported prophylaxis hemostatic medications, and three participants (33.3%) reported treatments for bleeds or short-term prophylaxis. The mean infusion/injection rate per year during the follow-up period to date was 28.5 (SD: 11.76) and the mean AIR was 56.41 (SD: 20.89) infusions/injections per year. All eight participants in the SoC cohort (with treatment data available) had a mean total prophylactic FVIII utilization of 97,500.00 (SD: 54,242.84) IUs and the mean total prophylactic FVIII utilization per participant per kg (IU/kg) was 1,247.68 (SD: 729.48), respectively. Only one (11.1%) participant had a record of non-factor utilization (e.g., emicizumab).

9.4.2.4 Clinical Outcome Assessments

No HJHS data was reported in the DHR extract for report data cut **(Appendix 2 Table 13),** though the study sponsor confirmed that the HJHS is being administered to participants who were enrolled and followed up in the study.

All 13 participants had baseline Haemo-QoL-A scores recorded. Of these, five (38.5%) had 6-month scores recorded. Baseline and 6-month scores were similar between the Roctavian and SoC cohorts. See **Appendix 2 Table 14** for details.

There was only one Roctavian participant and six SoC participants that reported baseline BPI-sf scores, with only two SoC participants (22.2%) reporting 6-month scores, see **Appendix 2 Table 15.**

9.4.2.5 Safety Events

No safety events were reported in the Roctavian or SoC cohorts at the time of the report (**Appendix 2 Table 16** and **Appendix 2 Table 17**).

9.4.2.6 Resumption of Prophylactic Treatment in Roctavian Cohort

No Roctavian cohort participants resumed prophylactic treatment after Roctavian administration (**Appendix 2 Table 18**).

9.4.3 Futility Analysis

A futility analysis was conducted to evaluate whether it was appropriate to continue enrolling patients in this study. Per the original protocol and SAP, discontinuation criteria were defined as enrollment of ≤33 participants in the Roctavian cohort and/or <67 participants in the SoC cohort after the 18-month recruitment period, unless there was an indication that recruitment was expected to considerably increase during the remainder of the recruitment period. As of 07 September 2025, enrollment remained well below these thresholds, with only four participants consented in the Roctavian cohort (which is 100% of the patients that were administered Roctavian in Germany after study start) and nine participants in the SoC cohort. Recruitment trends indicated that achieving the target sample size within the recruitment period was not feasible. Subsequent to the data cut, one additional Roctavian participant and 14 additional SoC participants enrolled in the study as of 02 March 2026 (total enrollment of four Roctavian participants and 23 SoC participants). Enrollment reflects all persons administered Roctavian in Germany since the start of the AbD through 02 March 2026. Factors influencing study enrollment included the limited number of sites certified for gene therapy administration (eight sites in Germany), delays in site activation (based on lack of site motivation due to lack of Roctavian patients) and limited uptake of Roctavian.

Enrollment numbers as of 02 March 2026 was still insufficient to meet the futility target of at least 33 participants in the Roctavian cohort and at least 67 participants in the SoC cohort.

9.4.4 Post-hoc Enrollment and Sample Size Calculations

The original sample size target for this study of 67 participants in the Roctavian cohort and 330 participants in the SoC cohort was determined using a negative binomial model to assess ABR, with a shifted null hypothesis of 0.5 and significance level alpha of 2.5%, with a one-sided test and power of at least 80%. A distribution of Roctavian versus SoC participants was assumed to be 1:5. Average exposure time (u_t) was assumed to be 1 year and ABR for the Roctavian and SoC cohorts was assumed to be 0.85 and 3.00, respectively. An overdispersion of 1.5 was assumed.

To investigate the sample size calculation further based on observed data three different scenarios were calculated based on the sample size at the end of the enrollment period:

1. **Observed power based on current sample size:** Based on the sample sizes at the end of the enrollment period (four Roctavian, 23 SoC) and maintaining the other assumptions from the sample size calculation (as reported above), the study was expected to have 14.0% power to observe an effect shifting the null hypothesis 0.5.

2. **Smallest effect size possible to observe:** Based on the sample sizes at the end of the enrollment period (four Roctavian, 23 SoC) and maintaining the other assumptions from the sample size calculation (as reported above), the study was expected to have 80% power to observe an effect size of 33 (or ABR rate of 0.09 in Roctavian cohort) assuming an ABR rate of 3.00 in the SoC cohort and shifting the null hypothesis 0.5.
3. **Enrollment period to achieve original sample size:** Finally, adjusting the rate of enrollment observed during the recruitment period (0.06 participants per site per month for the Roctavian cohort and 0.40 participants per site per month for the SoC cohort), an enrollment period through 27 July 2034 would have been required to meet the target sample size of 67 participants in the Roctavian cohort and 330 participants in the SoC cohort.

9.4.5 Subgroup Results

No subgroup analyses were conducted for this report due to small sample size.

9.4.6 Sensitivity Results

No sensitivity analyses were conducted for this report due to small sample size.

9.5 Adverse Events and Adverse Reactions

All reported adverse events and adverse reactions were included as safety events. No adverse events or adverse reactions occurred among study participants in the data utilized for this analysis.

10 DISCUSSION

10.1 Key Results

The findings of the 270-603 study highlight persistent operational barriers to site activation and participant enrollment for both the Roctavian and SoC cohorts. Despite identifying eight eligible sites who pursued the gene therapy certification, only six achieved activation in approximately 18-months, primarily due to administrative delays, staffing constraints, and low site motivation in the absence of potentially eligible Roctavian participants. In addition, PwSHA may not have been able to receive Roctavian right away given the requirement of health center and individual health insurance needing alignment as basis for prescription of Roctavian. Further, some of the eligible sites were still in the process of fulfilling the requirements for the quality of the application of medicinal products for advanced therapies in accordance with Section 136a(5) of the German Social Code, Book V (SGB V), which slowed enrollment. These operational constraints likely impacted the markedly low enrollment observed relative to target sample sizes, ultimately prompting futility.

Baseline demographic and clinical characteristics demonstrate broad comparability between the Roctavian and SoC cohorts, although small sample sizes limit robust inference. Participants in both cohorts exhibited similar mean and median ages and comorbidity profiles, including no target joints and no chronic liver disease in either population. The prophylaxis patterns observed at baseline were also similar. While FVIII utilization rates appeared higher in the Roctavian cohort, these estimates should be interpreted cautiously due to incomplete reporting and the very small analytic sample. Overall, the similarity in key baseline variables was a positive result, that propensity score adjustment methods, as specified in the protocol, would have been able account for measured/residual confounding or baseline differences between the two cohorts if the study had continued.

Early patterns in outcomes favored lower bleeding burden among Roctavian recipients, though the limited sample size prohibits definitive conclusions. Only one Roctavian participant experienced treated bleeds, yielding a mean ABR of 0.80 bleeds per year, whereas SoC participants exhibited a higher mean ABR of 1.64 bleeds per year. Similar pattern were observed for joint bleeds, which were the main bleed type in both cohorts. The proportion of participants experiencing zero bleeds was generally high across both cohorts. As expected due to the amount of follow-up time at the time of study closure, no Roctavian participant resumed prophylactic therapy post-Roctavian administration. All SoC participants continued prophylaxis, with substantial FVIII utilization documented. These findings preliminarily aligned with the expected hemostatic durability of gene therapy; however, the limited exposure time and minimal events necessitate cautious interpretation.

There were no reported adverse events or reactions of special interested or events leading to hospitalization in either cohort, although the small sample and limited follow-up should be noted. Regarding COAs, Haemo-QoL-A was well captured at baseline and among those participants who had six months of follow-up, while BPI-sf data were not as complete. Limited HJHS data entered in the registry limited characterization of joint health, although assessments were being conducted.

Taken together, these final results highlighted both the potential clinical value of Roctavian, and the methodological constraints imposed by slow enrollment, small sample size, and incomplete data capture.

10.2 Limitations

Due to the observational nature of this study, results represent a range of real-world practice in Germany, though results may be influenced by site heterogeneity (e.g., clinic structure, site specific clinical practices). The data utilized for this analysis were collected in the DHR. The DHR has the advantage of being an existing system with which German physicians are familiar and minimizes site burden for additional data collection specific to the AbD, though the DHR was more similar to a secondary data source for the purposes of this analysis. 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 was not controlled by the study sponsor and therefore the potential for missing data and/or implausible data values was possible. Data monitoring activities were intended to minimize missing data and implausible values in the analytic dataset, though data for the present analyses may be more prone to potential missing/erroneous data. To mitigate these limitations and presence of missing data, monitoring activities should be refined and adjusted as needed throughout the study conduct to ensure as complete data collection as possible.

Because of the small sample size and limited length of follow-up in this final analysis, all outcomes were reported descriptively and no comparative analyses or adjustment for confounding variables was conducted. As such, people in the Roctavian cohort and SoC cohort may differ in meaningful ways that affect their outcomes, although the baseline characteristics were broadly similar. Outcomes for the Roctavian cohort should be interpreted with caution, as they only reflect outcomes occurring within less than 12 months of Roctavian administration.

Although fields collected in the DHR were expanded to meet the needs of this study and data completeness was being assessed, the capture of some variables (e.g., bleeds) was not designed for the purposes of this study. As a result, there was the possibility of incomplete capture or variability in data granularity between sites. For example, although nine

participants met inclusion and exclusion criteria for the SoC cohort, there was one participant that did not have historical treatment data recorded in the DHR at the time of this analysis. Further, when reporting treated bleeds, it is expected that on-demand treatment is also reported, however no on-demand treatment was recorded in the data cut received for this analysis. In addition, due to the registry nature of the DHR, some of the baseline and historical data relied on recall of information or clinical history, where incomplete or inaccurate information may be present. To mitigate this limitation, SDV would have informed any future data extractions.

10.3 Interpretation

Findings from this final report should be interpreted with caution, given the limited sample size, short follow-up, and descriptive nature of the analyses. Observed outcomes and patterns in bleeding outcomes, treatment utilization, and COAs may change if enrollment was increased and longer-term data became available.

10.4 Generalizability

These results have limited external validity, as the enrolled population represents early initiators of Roctavian and a small subset of people receiving SoC treatment in Germany. Broader applicability to PwSHA will require larger sample size and longer follow-up.

11 CONCLUSIONS

Study recruitment for the Roctavian cohort reflected uptake of Roctavian in Germany, while SoC enrollment was scaled, relative to the Roctavian cohort. Uptake and enrollment in 270-603 was <10% of the sample size required per the sample size calculation conducted by the Institute for Quality and Efficiency in Health Care (IQWiG) and detailed in the study protocol, at the time of study closure. The limited uptake and small sample size constrains interpretability of the results and indicated that the study was futile in providing meaningful data on the comparative effectiveness of Roctavian to SoC hemostatic prophylaxis after the AbD specified recruitment period.

The study sponsor decided to voluntarily withdraw Roctavian from the German market (effective date of May 29, 2026); therefore, the 270-603 study was terminated. The study protocol and the SAP were not updated and the 18 month report was not submitted. On 02 April 2026 the G-BA decided that the post-marketing data collection for Roctavian was not being carried out. The restriction of prescribing authority was revoked. The sponsor submitted a final report to GBA in June 2026..[10,11] The decision to withdraw Roctavian was unrelated to any concerns regarding quality safety or efficacy of the product.

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13 APPENDICES

Appendix 1: HA Treatments

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

Treatment Type	Treatment Class	Treatment Name	Recommended Treatment Frequency and/or Dose
		Rurioctocog alfa pegol (Adynovi)	40-50 IU/kg twice weekly in 3–4-day intervals
		Turoctocog alfa pegol (Esperoct)	50 IU/kg every 4 days
	PD products	Voncento	20-40 IU/kg at intervals of 2-3 days
		Beriate	20-40 IU/kg at intervals of 2-3 days
		Octanate	20-40 IU/kg at intervals of 2-3 days
		Haemoctin	20-40 IU/kg at intervals of 2-3 days
		Faktor VIII SDH – Intersero	20-40 IU/kg at intervals of 2-3 days
		Haemate P	One IU of FVIII activity per kg body weight increases the circulating FVIII level by approximately 2.0 IU/dL. Individualize dosage based on weight, type and severity of hemorrhage, FVIII level, and presence of inhibitors.
Roctavian	N/A	Valoctocogene roxaparvovec (Roctavian)	6×10^{13} vg/kg body weight, administered as a single intravenous infusion

Appendix 2: RESULTS TABLES

Table 5. Study Sites and Status as of 02 March 2026

Site	PI	Activation Date/Reason if Not Activated	Ethics Committee Submission and Approval Dates	Dry SIV Date	CTA Status	ATMP-QS-RL	FPI
Vivantes Klinikum im Friedrichshain	Robert Klamroth	08 Jan 2025	No LEC submission required	09 Sep 2024	Fully executed 09 Jan 2025	Ready	09 Jan 2025
Universitäts-klinikum Regens-burg	Sonja Kramer	Under CTA review; Expected activation TBC	S: 07 Oct 2024 A: 09 Oct 2024	14 Nov 2024	Under review	In Prep	-
Universitätsklinikum Hamburg-Eppendorf	Florian Langer	19 Jan 2026	No LEC submission required	19 Jan 2026	Fully executed 15 Jan 2026	Ready	-
Universitäts-klinikum Frankfurt Goethe-Universität	Wolfgang Miesbach	01 Dec 2025	S: 17 Sep 2024 A: 23 Sep 2024	11 Sep 2024	Fully executed 01 Dec 2025	Ready	-
Universitäts-klinikum Bonn AoeR	Johannes Oldenburg	08 Nov 2024 (Favorable LEC vote determined	S: 25 Sep 2024 A: 08 Nov 2024	30 Sep 2024	Fully executed 31 Oct 2024	Ready	23 April 2025

Site	PI	Activation Date/Reason if Not Activated	Ethics Committee Submission and Approval Dates	Dry SIV Date	CTA Status	ATMP-QS-RL	FPI
		final site activation)					
Universitäts-klinikum Leipzig AoeR	Christian Pfrepper	26 Nov 2024	S: 30 Sep 2024 A: 22 Oct 2024	07 Nov 2024	Fully executed 26 Nov 2024	Ready	-
Medizinische Hoch-schule Hannover	Andreas Tiede	14 Mar 2025	S: 24 Sep 2024 A: 26 Sep 2024	10 Sep 2024	Fully executed 14 Mar 2025	Ready	-
Klinikum der Universität München	Patrick Moehnle	CTA finalization TBC, LEC submission pending	TBC	TBC	Currently under signatures	In Prep	-

Acronyms: A: approved; ATMP-QS-RL: ATMP-Qualitätssicherungs-Richtlinie; CTA: contract trial agreement; FPI: first patient in; LEC: Local Ethics Committee; PI: primary investigator; S: submitted; SIV, site initiation visit; TBC: to be completed

Table 6. Participant Disposition as of 02 March 2026

	Roctavian Cohort N (%)	**SoC Cohort N (%)**	**Total Participants N (%)**
Total Enrollment	4	9	13
Participants Remaining in Study	4	9	13
Participants on Treatment in Study	4	9	13
Participants Completed Study	0	0	0
Participants Lost to Follow-Up	0	0	0
Participants Withdrawn from Study	0	0	0
Participants Discontinuing Study Treatment	0	0	0



Table 7. Baseline Demographic Characteristics for Roctavian and SoC Cohorts

Measures	Roctavian Cohort		SoC Cohort	
	N=4		N=9	
	N	(%)	N	(%)
Age (years)	4	100.0%	9	100.0%
Mean	40.50		43.67	
SD	8.35		11.67	
Median	42.5		41	
Q1	34.5		38	
Q3	46.5		47	
Min	29		25	
Max	48		63	
Age categories (years)				
18-40	2	50.0%	3	33.3%
41-64	2	50.0%	6	66.7%
≥65	0	0.0%	0	0.0%
18-23	0	0.0%	0	0.0%
24-29	1	25.0%	1	11.1%
30-35	0	0.0%	1	11.1%
36-41	1	25.0%	3	33.3%
42-47	1	25.0%	2	22.2%
48-53	1	25.0%	0	0.0%
54-59	0	0.0%	1	11.1%
60-65	0	0.0%	1	11.1%
66-71	0	0.0%	0	0.0%
72-77	0	0.0%	0	0.0%
78-83	0	0.0%	0	0.0%
84-89	0	0.0%	0	0.0%
≥90	0	0.0%	0	0.0%
Age at first HA diagnosis (years)	2	50.0%	4	44.4%
Mean	0		0.75	
SD	0		0.96	
Median	0		0.5	

Measures	Roctavian Cohort		SoC Cohort	
	N=4		N=9	
	N	(%)	N	(%)
Q1	0		0	
Q3	0		1.5	
Min	0		0	
Max	0		2	
Age at first FVIII administration (years)	1	25.0%	0	0.0%
Mean	38		-	
SD	-		-	
Median	38		-	
Q1	38		-	
Q3	38		-	
Min	38		-	
Max	38		-	

Acronyms: FVIII: coagulation factor VIII; HA: hemophilia A; SD: standard deviation; SoC: standard of care Note: age at first HA diagnosis and age at first FVIII administration was missing for some participants.



Table 8. Baseline Clinical Characteristics for Roctavian and SoC Cohorts

Measures	Roctavian Cohort		SoC Cohort	
	N=4		N=9	
	N	(%)	N	(%)
Height (cm)	4	100.0%	8	88.9%
Mean	189.75		178.63	
SD	7.85		5.64	
Median	193.5		179.5	
Q1	185.5		174.5	
Q3	194		181.5	
Min	178		170	
Max	194		188	
Weight (kg)	4	100.0%	8	88.9%
Mean	90.75		79.63	
SD	18.41		9.86	
Median	87		79.5	
Q1	76		71	
Q3	105.5		86	
Min	75		68	
Max	114		96	
BMI	4	100.0%	8	88.9%
<18.50	0	0.0%	0	0.0%
18.50 - <25.00	2	50.0%	5	55.6%
25.00 - <30.00	1	25.0%	3	33.3%
≥30.00	1	25.0%	0	0.0%
HCV infection				
No infection	1	25.0%	0	0.0%
Active and/or cured infection	1	25.0%	0	0.0%
Unknown	2	50.0%	9	100.0%
Chronic liver disease				
Liver fibrosis	0	0.0%	0	0.0%

Measures	Roctavian Cohort		SoC Cohort	
	N=4		N=9	
	N	(%)	N	(%)
Liver cirrhosis	0	0.0%	0	0.0%
Not specified/unknown	4	100.0%	9	100.0%
Other comorbidities				
Malignancy	0	0.0%	0	0.0%
Hypertension	0	0.0%	0	0.0%
Osteoporosis	0	0.0%	0	0.0%
Targeted joints				
Yes	0	0.0%	0	0.0%
No	4	100.0%	9	100.0%
Unknown	0	0.0%	0	0.0%
Number of target joints	0	0.0%	0	0.0%
Mean	-		-	
SD	-		-	
Median	-		-	
Q1	-		-	
Q3	-		-	
Min	-		-	
Max	-		-	
Prophylaxis type				
FVIII only	4	100.0%	7	77.8%
Non-factor products only (e.g., emicizumab)	0	0.0%	0	0.0%
FVIII and non-factor products	0	0.0%	1	11.1%
Missing			1*	11.1%
SoC switch				
No change	4	100.0%	8	88.9%
Change in 1 year prior to index	0	0.0%	0	0.0%
SHL to EHL	-	-	0	0.0%
SHL to emicizumab	-	-	0	0.0%
EHL to emicizumab	-	-	0	0.0%
Emicizumab to SHL	-	-	0	0.0%

Measures	Roctavian Cohort		SoC Cohort	
	N=4		N=9	
	N	(%)	N	(%)
Emicizumab to EHL	-	-	0	0.0%
Emicizumab to PD	-	-	0	0.0%
PD to emicizumab	-	-	0	0.0%
AAV5 antibody status				
AAV5 negative	4	100.0%	0	0.0%
AAV5 positive	0	0.0%	0	0.0%
Use of immunosuppression				
Yes	0	0.0%	0	0.0%
No	4	100.0%	9	100.0%
FVIII infusion rate (number of infusions/year), SHL	0	0.00%	1	11.1%
Mean	-		182.63	
SD	-		.	
Median	-		182.63	
Q1	-		182.63	
Q3	-		182.63	
Min	-		182.63	
Max	-		182.63	
FVIII infusion rate (number of infusions/year), EHL	4	100.0%	7	77.8%
Mean	155.21	.	115.22	
SD	141.80	.	39.27	
Median	100.88	.	108.22	
Q1	75.61	.	78.78	
Q3	234.80	.	146.10	
Min	53.83	.	58.44	
Max	365.25	.	170.45	
FVIII infusion rate (number of infusions/year), PD	0	0.0%	0	0.0%
Mean	-		-	
SD	-		-	
Median	-		-	

Measures	Roctavian Cohort		SoC Cohort	
	N=4		N=9	
	N	(%)	N	(%)
Q1	-		-	
Q3	-		-	
Min	-		-	
Max	-		-	
FVIII infusion rate (number of infusions/year), emicizumab	0	0.0%	1	11.1%
Mean	-		24.35	
SD	-		-	
Median	-		-	
Q1	-		24.35	
Q3	-		24.35	
Min	-		24.35	
Max	-		24.35	
Annualized baseline FVIII utilization (IU/kg/year), bleeds	0	0.0%	1	11.1%
Mean	-		1,560.90	
SD	-		.	
Median	-		1,560.90	
Q1	-		1,560.90	
Q3	-		1,560.90	
Min	-		1,560.90	
Max	-		1,560.90	
Annualized baseline FVIII utilization (IU/kg/year), prophylaxis	4	100.0%	8	88.9%
Mean	7,611.04	.	4,126.59	
SD	7,940.86	.	1,878.02	
Median	4,094.80	.	3,890.84	
Q1	3,284.68	.	2,758.27	
Q3	11,937.40	.	5,686.94	
Min	2,774.55	.	1,425.37	
Max	19,480.00	.	6,915.25	
Annualized baseline FVIII utilization (IU/kg/year), short-term prophylaxis	0	0.0%	0	0.0%

Measures	Roctavian Cohort		SoC Cohort	
	N=4		N=9	
	N	(%)	N	(%)
Mean	-		-	
SD	-		-	
Median	-		-	
Q1	-		-	
Q3	-		-	
Min	-		-	
Max	-		-	
Annualized baseline FVIII utilization (IU/kg/year), surgery	0	0.0%	0	0.0%
Mean	-		-	
SD	-		-	
Median	-		-	
Q1	-		-	
Q3	-		-	
Min	-		-	
Max	-		-	
Annualized baseline FVIII utilization (IU/kg/year), ITT	0	0.0%	0	0.0%
Mean	-		-	
SD	-		-	
Median	-		-	
Q1	-		-	
Q3	-		-	
Min	-		-	
Max	-		-	
Annualized baseline FVIII utilization (IU/kg/year), other/unknown reason	0	0.0%	0	0.0%
Mean	-		-	
SD	-		-	
Median	-		-	
Q1	-		-	
Q3	-		-	
Min	-		-	

Measures	Roctavian Cohort		SoC Cohort	
	N=4		N=9	
	N	(%)	N	(%)
Max	-		-	
Baseline ABR, overall				
Mean	0.00		1.40	
SD	0.00		4.20	
Median	0.00		0.00	
Q1	0.00		0.00	
Q3	0.00		0.00	
Min	0.00		0.00	
Max	0.00		12.59	
Baseline treated ABR				
Mean	0.00		1.40	
SD	0.00		4.20	
Median	0.00		0.00	
Q1	0.00		0.00	
Q3	0.00		0.00	
Min	0.00		0.00	
Max	0.00		12.59	
Baseline major ABR				
Mean	0.00		0.00	
SD	0.00		0.00	
Median	0.00		0.00	
Q1	0.00		0.00	
Q3	0.00		0.00	
Min	0.00		0.00	
Max	0.00		0.00	
Baseline life-threatening ABR				
Mean	0.00		0.00	
SD	0.00		0.00	
Median	0.00		0.00	
Q1	0.00		0.00	
Q3	0.00		0.00	
Min	0.00		0.00	

Measures	Roctavian Cohort		SoC Cohort	
	N=4		N=9	
	N	(%)	N	(%)
Max	0.00		0.00	
Baseline joint ABR				
Mean	0.00		0.00	
SD	0.00		0.00	
Median	0.00		0.00	
Q1	0.00		0.00	
Q3	0.00		0.00	
Min	0.00		0.00	
Max	0.00		0.00	

Acronyms: AAV5: adeno-associated virus type 5; ABR: annualized bleeding rate; BMI: body mass index; EHL: extended half-life; FVIII: coagulation factor VIII; HCV: hepatitis C virus; ITT: immune tolerance therapy; IU: international units; kg: kilogram; mL: milliliters; PD: plasma-derived; SD: standard deviation; SHL: standard half-life; SoC: standard of care
*Note: One participant does not have treatment history information to confirm prophylaxis type, but was confirmed to be on FVIII as part of the patient consent process

Table 9. Treated ABR for Roctavian and SoC Cohorts

Measures	Roctavian Cohort		SoC Cohort	
	N=4		N=9	
	N	(%)	N	(%)
Follow-up time (days) from enrollment to data cut*	4	100.0%	9	100.0%
Mean	165.25		212.44	
SD	87.88		20.26	
Median	183		206	
Q1	95.5		193	
Q3	235		235	
Min	53		193	
Max	242		235	
Number of participants with at least 6 months of follow-up from enrollment to data cut	2	50.0%	9	100.0%
Treated ABR				
Mean	0.80		1.64	
SD	1.60		2.91	
Median	0.00		0.00	
Q1	0.00		0.00	
Q3	1.60		1.55	
Min	0.00		0.00	
Max	3.20		7.57	
N bleeding events	2		8	
N patients with bleeding events				
1 bleeding event	0	0.0%	1	11.1%
2-5 bleeding events	1	25.0%	2	22.2%
6-9 bleeding events	0	0.0%	0	0.0%

Acronyms: ABR: annualized bleeding rate; SoC: standard of care; SD: standard deviation
*7 September 2025 was the data cut date for the final analysis.



Table 10. Major, Life-Threatening, and Joint ABR for Roctavian and SoC Cohorts

Measures	Roctavian Cohort		SoC Cohort	
	N=4		N=9	
	N	(%)	N	(%)
Major ABR				
Mean	0.00		0.00	
SD	0.00		0.00	
Median	0.00		0.00	
Q1	0.00		0.00	
Q3	0.00		0.00	
Min	0.00		0.00	
Max	0.00		0.00	
N bleeding events	0	0.0%	0	0.0%
N patients with bleeding events				
1 bleeding event	0	0.0%	0	0.0%
2-5 bleeding events	0	0.0%	0	0.0%
6-9 bleeding events	0	0.0%	0	0.0%
Life-threatening ABR				
Mean	0.00		0.00	
SD	0.00		0.00	
Median	0.00		0.00	
Q1	0.00		0.00	
Q3	0.00		0.00	
Min	0.00		0.00	
Max	0.00		0.00	
N bleeding events	0	0.0%	0	0.0%
N patients with bleeding events				
1 bleeding event	0	0.0%	0	0.0%
2-5 bleeding events	0	0.0%	0	0.0%
6-9 bleeding events	0	0.0%	0	0.0%
Joint ABR	1	25.0%	2	22.2%
Mean	0.40		1.47	
SD	0.80		2.96	
Median	0.00		0.00	

Measures	Roctavian Cohort		SoC Cohort	
	N=4		N=9	
	N	(%)	N	(%)
Q1	0.00		0.00	
Q3	0.80		0.00	
Min	0.00		0.00	
Max	1.60		7.57	
N bleeding events	1		7	
N patients with bleeding events				
1 bleeding event	1	25.00%	0	0.00%
2-5 bleeding events	0	0.00%	2	22.22%
6-9 bleeding events	0	0.00%	0	0.00%

Acronyms: ABR: annualized bleeding rate; SoC: standard of care; SD: standard deviation



Table 11. Proportion of Participants with Zero Bleeds, Roctavian and SoC Cohorts

Measures	Roctavian Cohort		SoC Cohort	
	N=4		N=9	
	N	(%)	N	(%)
Participants with zero treated bleeds	3	75.0%	6	66.7%
Participants with zero major bleeds	4	100.0%	9	100.0%
Participants with zero life-threatening bleeds	4	100.0%	9	100.0%
Participants with zero joint bleeds	3	75.0%	7	77.8%

Acronyms: SoC: standard of care



Table 12. Hemostatic Medication Use for Roctavian and SoC Cohorts (Treatment Policy Estimand)

Measures	Roctavian Cohort		SoC Cohort	
	N=4		N=9	
	N	(%)	N	(%)
Participants with any hemostatic medication use	4	100.0%	8	88.9%
Participants with hemostatic medication use for bleeds or short-term prophylaxis	1	25.0%	3	33.3%
Infusion/injection rate (number of infusions or injections/year)	4	100%	8	88.9%
Mean	10.57		28.50	
SD	7.87		11.76	
Median	8.64		24.5	
Q1	4.5		20	
Q3	16.64		37	
Min	4		16	
Max	21		49	
AIR	4	100.0%	8	88.9%
Mean	78.89		56.41	
SD	29.31		20.89	
Median	83.93		52.32	
Q1	54.87		41.30	
Q3	102.91		70.55	
Min	43.33		29.22	
Max	104.36		93.70	
Prophylactic use				
Total prophylactic FVIII utilization (IU)	4	100.0%	8	88.9%
Mean	41,500		97,500	
SD	25,592.97		54,242.84	
Median	42,500		96,500	
Q1	19,500		60,000	
Q3	63,500		151,000	

Measures	Roctavian Cohort		SoC Cohort	
	N=4		N=9	
	N	(%)	N	(%)
Min	16,000		7,000	
Max	65,000		158,000	
Total prophylactic FVIII utilization per patient per kg (IU/kg)	4	100.0%	8	88.9%
Mean	456.45		1,247.68	
SD	283.88		729.48	
Median	403.64		1,161.46	
Q1	225.22		800.70	
Q3	687.69		1,824.10	
Min	213.33		85.37	
Max	805.19		2,323.53	
Total prophylactic emicizumab utilization (mg)	0	0.0%	1	11.1%
Mean	-		3,570	
SD	-		-	
Median	-		3,570	
Q1	-		3,570	
Q3	-		3,570	
Min	-		3,570	
Max	-		3,570	
Total prophylactic emicizumab utilization per patient per kg (mg/kg)	0	0.0%	1	11.1%
Mean	-		43.54	
SD	-		-	
Median	-		43.54	
Q1	-		43.54	
Q3	-		43.54	
Min	-		43.54	
Max	-		43.54	
On-demand use for bleeds				
Total on-demand FVIII utilization for bleed (IU)	0	0.0%	0	0.0%
Mean	-		-	

Measures	Roctavian Cohort		SoC Cohort	
	N=4		N=9	
	N	(%)	N	(%)
SD	-		-	
Median	-		-	
Q1	-		-	
Q3	-		-	
Min	-		-	
Max	-		-	
Total on-demand FVIII utilization per patient per kg for bleed (IU/kg)	0	0.0%	0	0.0%
Mean	-		-	
SD	-		-	
Median	-		-	
Q1	-		-	
Q3	-		-	
Min	-		-	
Max	-		-	

Acronyms: AIR: annualized infusion rate; FVIII: coagulation factor VIII; IU: international units; kg: kilogram; mg: milligram; SD: standard deviation; SoC: standard of care



Table 13. COAs for Roctavian and SoC Cohorts – HJHS

Measures	Roctavian Cohort		SoC Cohort	
	N=4		N=9	
	N	(%)	N	(%)
Baseline				
Left elbow	0	0.0%	0	0.0%
Mean	-		-	
SD	-		-	
Median	-		-	
Q1	-		-	
Q3	-		-	
Min	-		-	
Max	-		-	
Right elbow	0	0.0%	0	0.0%
Mean	-		-	
SD	-		-	
Median	-		-	
Q1	-		-	
Q3	-		-	
Min	-		-	
Max	-		-	
Left knee	0	0.0%	0	0.0%
Mean	-		-	
SD	-		-	
Median	-		-	
Q1	-		-	
Q3	-		-	
Min	-		-	
Max	-		-	
Right knee	0	0.0%	0	0.0%
Mean	-		-	
SD	-		-	
Median	-		-	
Q1	-		-	

Measures	Roctavian Cohort		SoC Cohort	
	N=4		N=9	
	N	(%)	N	(%)
Q3	-		-	
Min	-		-	
Max	-		-	
Left ankle	0	0.0%	0	0.0%
Mean	-		-	
SD	-		-	
Median	-		-	
Q1	-		-	
Q3	-		-	
Min	-		-	
Max	-		-	
Right ankle	0	0.0%	0	0.0%
Mean	-		-	
SD	-		-	
Median	-		-	
Q1	-		-	
Q3	-		-	
Min	-		-	
Max	-		-	
Global gait score	0	0.0%	0	0.0%
Mean	-		-	
SD	-		-	
Median	-		-	
Q1	-		-	
Q3	-		-	
Min	-		-	
Max	-		-	
Total score	0	0.0%	0	0.0%
Mean	-		-	
SD	-		-	
Median	-		-	
Q1	-		-	

Measures	Roctavian Cohort		SoC Cohort	
	N=4		N=9	
	N	(%)	N	(%)
Q3	-		-	
Min	-		-	
Max	-		-	
6 month				
Left elbow	0	0.0%	0	0.0%
Mean	-		-	
SD	-		-	
Median	-		-	
Q1	-		-	
Q3	-		-	
Min	-		-	
Max	-		-	
Right elbow	0	0.0%	0	0.0%
Mean	-		-	
SD	-		-	
Median	-		-	
Q1	-		-	
Q3	-		-	
Min	-		-	
Max	-		-	
Left knee	0	0.0%	0	0.0%
Mean	-		-	
SD	-		-	
Median	-		-	
Q1	-		-	
Q3	-		-	
Min	-		-	
Max	-		-	
Right knee	0	0.0%	0	0.0%
Mean	-		-	
SD	-		-	
Median	-		-	

Measures	Roctavian Cohort		SoC Cohort	
	N=4		N=9	
	N	(%)	N	(%)
Q1	-		-	
Q3	-		-	
Min	-		-	
Max	-		-	
Left ankle	0	0.0%	0	0.0%
Mean	-		-	
SD	-		-	
Median	-		-	
Q1	-		-	
Q3	-		-	
Min	-		-	
Max	-		-	
Right ankle	0	0.0%	0	0.0%
Mean	-		-	
SD	-		-	
Median	-		-	
Q1	-		-	
Q3	-		-	
Min	-		-	
Max	-		-	
Global gait score	0	0.0%	0	0.0%
Mean	-		-	
SD	-		-	
Median	-		-	
Q1	-		-	
Q3	-		-	
Min	-		-	
Max	-		-	
Total score	0	0.0%	0	0.0%
Mean	-		-	
SD	-		-	
Median	-		-	

Measures	Roctavian Cohort		SoC Cohort	
	N=4		N=9	
	N	(%)	N	(%)
Q1	-		-	
Q3	-		-	
Min	-		-	
Max	-		-	

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



Table 14. COAs for Roctavian and SoC Cohorts – Haemo-QoL-A

Measures	Roctavian Cohort		SoC Cohort	
	N=4		N=9	
	N	(%)	N	(%)
Baseline				
Physical functioning	4	100.0%	9	100.0%
Mean	3.81		3.04	
SD	0.81		1.10	
Median	4		3.22	
Q1	3.28		2	
Q3	4.33		3.44	
Min	2.67		1.78	
Max	4.56		5	
Role functioning	4	100.0%	9	100.0%
Mean	4.41		3.78	
SD	0.28		0.66	
Median	4.32		4	
Q1	4.23		3.18	
Q3	4.59		4.18	
Min	4.18		2.82	
Max	4.82		4.82	
Worry	4	100.0%	9	100.0%
Mean	4.8		3.96	
SD	0.16		0.92	
Median	4.8		4.2	
Q1	4.7		3.8	
Q3	4.9		4.4	
Min	4.6		2.2	
Max	5		5	
Consequences of bleeding	4	100.0%	9	100.0%
Mean	4.86		3.84	
SD	0.16		1.01	
Median	4.86		4.29	
Q1	4.71		3.29	

Measures	Roctavian Cohort		SoC Cohort	
	N=4		N=9	
	N	(%)	N	(%)
Q3	5		4.43	
Min	4.71		1.71	
Max	5		5	
Emotional impact	4	100.0%	9	100.0%
Mean	4.17		3.93	
SD	0.65		0.88	
Median	4.25		4.17	
Q1	3.67		3.33	
Q3	4.67		4.67	
Min	3.33		2.33	
Max	4.83		4.83	
Treatment concerns	4	100.0%	9	100.0%
Mean	4.33		3.70	
SD	0.61		1.09	
Median	4.33		4	
Q1	3.83		3.33	
Q3	4.83		4.33	
Min	3.67		1.33	
Max	5		5	
Total score	4	100.0%	9	100.0%
Mean	26.37		22.24	
SD	1.85		4.85	
Median	26.14		23.96	
Q1	25.00		19.22	
Q3	27.75		25.30	
Min	24.45		13.36	
Max	28.76		28.56	
6 month				
Physical functioning	2	50.0%	3	33.3%
Mean	4.28		3.44	
SD	0.55		0.95	
Median	4.28		3.56	

Measures	Roctavian Cohort		SoC Cohort	
	N=4		N=9	
	N	(%)	N	(%)
Q1	3.89		2.44	
Q3	4.67		4.33	
Min	3.89		2.44	
Max	4.67		4.33	
Role functioning	2	50.0%	3	33.3%
Mean	4.68		3.88	
SD	0.32		0.92	
Median	4.68		4	
Q1	4.45		2.91	
Q3	4.91		4.73	
Min	4.45		2.91	
Max	4.91		4.73	
Worry	2	50.0%	3	33.3%
Mean	4.6		4	
SD	0.57		1.25	
Median	4.6		4.4	
Q1	4.2		2.6	
Q3	5		5	
Min	4.2		2.6	
Max	5		5	
Consequences of bleeding	2	50.0%	3	33.3%
Mean	4.36		3.76	
SD	0.10		0.79	
Median	4.36		4.14	
Q1	4.29		2.86	
Q3	4.43		4.29	
Min	4.29		2.86	
Max	4.43		4.29	
Emotional impact	2	50.0%	3	33.3%
Mean	4.08		3.94	
SD	0.59		1.13	
Median	4.08		4.33	

Measures	Roctavian Cohort		SoC Cohort	
	N=4		N=9	
	N	(%)	N	(%)
Q1	3.67		2.67	
Q3	4.5		4.83	
Min	3.67		2.67	
Max	4.5		4.83	
Treatment concerns	2	50.0%	3	33.3%
Mean	4.33		3.56	
SD	0.94		0.51	
Median	4.33		3.67	
Q1	3.67		3	
Q3	5		4	
Min	3.67		3	
Max	5		4	
Total score	2	50.0%	3	33.3%
Mean	26.33		22.59	
SD	3.07		4.77	
Median	26.33		24.57	
Q1	24.16		17.14	
Q3	28.50		26.04	
Min	24.16		17.14	
Max	28.50		26.04	

Acronyms: COA: clinical outcome assessment; SD: standard deviation; SoC: standard of care



Table 15. COAs for Roctavian and SoC Cohorts – BPI-sf

Measures	Roctavian Cohort		SoC Cohort	
	N=4		N=9	
	N	(%)	N	(%)
Baseline				
Pain intensity (Question 3)	1	25.0%	6	66.7%
Mean	3		5.5	
SD	-		2.07	
Median	3		6.5	
Q1	3		4	
Q3	3		7	
Min	3		2	
Max	3		7	
Pain intensity (Question 4)	1	25.0%	6	66.7%
Mean	0		3	
SD	-		2.68	
Median	0		2	
Q1	0		1	
Q3	0		4	
Min	0		1	
Max	0		8	
Pain intensity (Question 5)	1	25.0%	6	66.7%
Mean	1		3.5	
SD	-		1.38	
Median	1		4	
Q1	1		3	
Q3	1		4	
Min	1		1	
Max	1		5	
Pain intensity (Question 6)	1	25.0%	6	66.7%
Mean	1		3	
SD	-		2.19	
Median	1		3.5	
Q1	1		1	

Measures	Roctavian Cohort		SoC Cohort	
	N=4		N=9	
	N	(%)	N	(%)
Q3	1		4	
Min	1		0	
Max	1		6	
Pain interference (Question 9)	1	25.0%	6	66.7%
Mean	1.43		4.05	
SD	-		2.59	
Median	1.43		5	
Q1	1.43		1.86	
Q3	1.43		6.14	
Min	1.43		0	
Max	1.43		6.29	
6 Month				
Pain intensity (Question 3)	0	0.0%	2	22.2%
Mean	-		8	
SD	-		2.83	
Median	-		8	
Q1	-		6	
Q3	-		10	
Min	-		6	
Max	-		10	
Pain intensity (Question 4)	0	0.0%	2	22.2%
Mean	-		4	
SD	-		2.83	
Median	-		4	
Q1	-		2	
Q3	-		6	
Min	-		2	
Max	-		6	
Pain intensity (Question 5)	0	0.0%	2	22.2
Mean	-		5.5	
SD	-		3.54	
Median	-		5.5	

Measures	Roctavian Cohort		SoC Cohort	
	N=4		N=9	
	N	(%)	N	(%)
Q1	-		3	
Q3	-		8	
Min	-		3	
Max	-		8	
Pain intensity (Question 6)	0	0.0%	2	22.2%
Mean	-		5.5	
SD	-		4.95	
Median	-		5.5	
Q1	-		2	
Q3	-		9	
Min	-		2	
Max	-		9	
Pain interference (Question 9)	0	0.0%	2	22.2%
Mean	-		3.79	
SD	-		4.34	
Median	-		3.79	
Q1	-		0.71	
Q3	-		6.86	
Min	-		0.71	
Max	-		6.86	

Acronyms: BPI-sf: Brief Pain Inventory - short form; COA: clinical outcome assessment; SD: standard deviation; SoC: standard of care



Table 16. Safety Outcomes for Roctavian and SoC Cohorts

Measures	Roctavian Cohort		SoC Cohort	
	N=4		N=9	
	N	(%)	N	(%)
All-cause death	0	0.0%	0	0.0%
Death due to bleeding	0	0.0%	0	0.0%
AEs leading to hospitalization - any cause	0	0.0%	0	0.0%
AEs leading to hospitalization - connected to hemophilia treatment	0	0.0%	0	0.0%
AEs leading to death - any cause	0	0.0%	0	0.0%
AEs leading to death - connected to hemophilia treatment	0	0.0%	0	0.0%
Development of FVIII inhibitors	0	0.0%	0	0.0%
Thromboembolic events - any cause	0	0.0%	0	0.0%
Thromboembolic events - connected to hemophilia treatment	0	0.0%	0	0.0%
Malignant neoplasms	0	0.0%	0	0.0%
Severe liver disease - any cause	0	0.0%	0	0.0%
Severe liver disease - connected to hemophilia treatment	0	0.0%	0	0.0%

Acronyms: AE: adverse event; FVIII: coagulation factor VIII; SoC: standard of care

Table 17. Free Text Safety Events for Roctavian and SoC Cohorts

Measures	Roctavian Cohort		SoC Cohort	
	N=4		N=9	
	N	(%)	N	(%)
Free Text Safety Event				
None	-	-	-	-

Acronyms: SoC: standard of care



Table 18. Time to Resumption of Prophylactic Treatment for Roctavian Cohort tri

Measures	Roctavian Cohort N=4	
	N	(%)
Patients who resumed prophylactic treatment	0	0.0%
Time to resumption of prophylactic treatment (days)		
Mean	-	
SD	-	
Median	-	
Q1	-	
Q3	-	
Min	-	
Max	-	
Number of infusions/injections 3 months after resumption of prophylaxis	0	0.0%
SHL		
Mean	-	
SD	-	
Median	-	
Q1	-	
Q3	-	
Min	-	
Max	-	
EHL		
Mean	-	
SD	-	
Median	-	
Q1	-	
Q3	-	
Min	-	
Max	-	
Emicizumab		
Mean	-	
SD	-	
Median	-	

Measures	Roctavian Cohort N=4	
	N	**(%)**
Q1	-	
Q3	-	
Min	-	
Max	-	
PD		
Mean	-	
SD	-	
Median	-	
Q1	-	
Q3	-	
Min	-	
Max	-	
Number of infusions/injections 6 months after resumption of prophylaxis	0	0.0%
SHL		
Mean	-	
SD	-	
Median	-	
Q1	-	
Q3	-	
Min	-	
Max	-	
EHL		
Mean	-	
SD	-	
Median	-	
Q1	-	
Q3	-	
Min	-	
Max	-	
Emicizumab		
Mean	-	
SD	-	
Median	-	
Q1	-	

Measures	Roctavian Cohort N=4	
	N	(%)
Q3	-	
Min	-	
Max	-	
PD		
Mean	-	
SD	-	
Median	-	
Q1	-	
Q3	-	
Min	-	
Max	-	
Total FVIII dose 3 months after resumption of prophylaxis	0	0.0%
Mean	-	
SD	-	
Median	-	
Q1	-	
Q3	-	
Min	-	
Max	-	
Total FVIII dose 6 months after resumption of prophylaxis	0	0.0%
Mean	-	
SD	-	
Median	-	
Q1	-	
Q3	-	
Min	-	
Max	-	
Frequency of infusions/injections 3 months after resumption of prophylaxis	0	0.0%
2x per day	0	0.0%
Daily	0	0.0%
Every 2nd day	0	0.0%
Every 3rd day	0	0.0%

Measures	Roctavian Cohort N=4	
	N	(%)
3x per week	0	0.0%
2x per week	0	0.0%
Weekly	0	0.0%
Every 10 days	0	0.0%
Every 2 weeks	0	0.0%
Monthly	0	0.0%
Frequency of infusions/injections 6 months after resumption of prophylaxis		
2x per day	0	0.0%
Daily	0	0.0%
Every 2nd day	0	0.0%
Every 3rd day	0	0.0%
3x per week	0	0.0%
2x per week	0	0.0%
Weekly	0	0.0%
Every 10 days	0	0.0%
Every 2 weeks	0	0.0%
Monthly	0	0.0%

Acronyms: EHL: extended half-life; PD: plasma-derived; SHL: standard half-life; SoC: standard of care