1. NIS INFORMATION

Title	Non-interventional study of long-term treatment with Haemoctin SDH
NIS number	Biotest NIS-016
Version identifier of the final study report	Final Version 1.0
Date of last version of the final study report	08-Dec-2023
ENCePP register number	13728
Active substance	Coagulation factor VIII ATC-Code: B02BD02
Medicinal product	Haemoctin SDH
Marketing authorization holder(s)	Biotest AG Landsteinerstr. 5 63303 Dreieich, Germany
Research question and objectives	The aim of this NIS was to document the long-term effectiveness of Haemoctin SDH in the prevention of bleedings and to determine the quality of life (QoL). The following research questions were examined: • What are the factors influencing the risk of bleeding over the time of treatment? • What are the factors influencing the risk to develop factor VIII inhibitors during treatment with Haemoctin SDH? • Can these inhibitors be further characterized? • What impact has a longstanding regular treatment with Haemoctin SDH on QoL?
Countries of study	Germany, Hungary, Austria
Author	[redacted] Biotest AG

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3. ABSTRACT

Title	**Non-interventional study of long-term treatment with Haemoctin SDH**
Keywords	Non-interventional study; long-term observation; hemophilia A; Haemoctin SDH; factor VIII deficiency; factor VIII inhibitor; quality of life
Rationale and background	Haemoctin SDH is a factor VIII (FVIII) preparation derived from human plasma purified by chromatography. Haemoctin SDH is approved for prevention and treatment of innate and acquired FVIII deficiencies. Also, patients with a FVIII inhibitor can be treated with Haemoctin SDH. Details are given in the summary of product characteristics (SmPC) of Haemoctin SDH. The stabilization of the FVIII molecule is carried out by the natural carrier protein von Willebrand factor. There is no need for the addition of auxiliary stabilizers such as sucrose or human serum albumin. Hemophilia A is an inherited, chronic bleeding disorder and patients have to be treated lifelong with FVIII concentrates. Most children and adolescents are treated prophylactically in industrialized countries. Prophylaxis has the goal to avoid bleedings, in order to guarantee the patient a high quality of life (QoL). For patients who have started in childhood with the prophylaxis, this treatment is extended in adulthood. Prophylactic treatment consists of regular FVIII applications, usually three times a week. With this study long-term data were generated. The total observation time of a previous study with Haemoctin combined with the present study covers a period of up to about 24 years and enabled unique long-term data to be obtained from several patients. This non-interventional study (NIS) allowed adapting the documentation to the current guidance for observational studies and adjusted focus of the objectives.
Research question and objectives	The aim of this NIS was to generate long-term data on the effectiveness in bleeding prevention and on QoL. The following questions were examined: • What are the factors influencing the risk of bleeding over the time of treatment? • What are the factors influencing the risk to develop FVIII inhibitors during treatment with Haemoctin SDH? • Can these inhibitors be further characterized? • What impact has a longstanding regular treatment with Haemoctin SDH on QoL?
Study design	Non-interventional, prospective and retrospective, single-arm study

Setting	11 German, 7 Hungarian and 1 (with 2 sub-centers, i.e., children and adults) Austrian hemophilia centers. Documentation period: Oct-2016 (initiation of first study site) to 31-Dec-2022 (end of data collection)
Patients and study size	All Patients Set (APS): 84 patients Full Analysis Set (FAS): 64 patients Safety Analysis Set (SAF): 80 patients Pooled Safety Analysis Set (PSAF): 48 patients
Variables and data sources	Demographic data; family history of hemophilia A; medical history, health status, concomitant diseases, previous treatment, Haemoctin SDH treatment, concomitant treatment, number, severity and location of bleedings, patient-reported QoL; occurrence and immunological characterization of inhibitors; adverse events (AEs); assessments of effectiveness, tolerability and handling by patient and investigator; patient's activity and days of illness; reasons for stopping documentation; arthropathy progress (optional)
Results	**Study population** Overall, 84 patients were enrolled in this NIS (APS), 41 in Germany, 37 in Hungary and 6 in Austria. The SAF, used for most analyses, included 80 patients. All patients included in the SAF were male. At baseline in the SAF, the median age was 38 years (range 2 to 81 years). The median age at diagnosis of hemophilia A was 1 year (range 0 to 70 years) and the median time since hemophilia A diagnosis was 35.5 years (range 0 to 75 years). At the beginning of the NIS, 8 patients had FVIII inhibitors and 72 patients had no FVIII inhibitors. The pooled population of the previous and current NIS (PSAF) included 48 patients. **Treatment** The predominant treatment regimen in the NIS was "prophylaxis overall" (75/80 patients), while only 3/80 patients received on demand treatment. Within the prophylaxis group, 26/75 patients received "prophylaxis ≥20 IU/kg 3 times per week" and 14/75 "prophylaxis <20 IU/kg 3 times per week". No major differences in treatment were observed between the participating countries. Likewise, in the PSAF, 47/48 patients received prophylactic treatment and only 1/48 patient on demand treatment. **Effectiveness** Based solely on the Joint-Bleeds eCRF instrument, patients had a median ABR of 0.12 (FAS). The median ABR in the "Prophylaxis <20 IU/kg 3 times/week" subgroup was higher than in the "Prophylaxis ≥20 IU/kg 3 times/week" subgroup (2.47 vs. 0.0). The median ABR of PUPs and of PTPs was identical (0.24). Based on the eCRF Bleeding Page that included all types of bleeding, patients had a median extended ABR of 0.72 (FAS). The median

	extended ABR in the "Prophylaxis <20 IU/kg 3 times/week" subgroup was higher than in the "Prophylaxis ≥20 IU/kg 3 times/week" subgroup (2.67 vs. 0.87). The median extended ABR of PUPs was lower than of PTPs (0.24 vs. 0.88). In the total PSAF including patient data from the previous NIS, the median extended ABR, based on the eCRF Bleeding Page, was 14.59. Formation of FVIII inhibitors was not observed during the present study. Regarding quality of life, the VAS suggested a mild improvement in patient-reported health in Year 1 and 2 (SAF). The assessments of treatment effectiveness, tolerance, handling of Haemoctin SDH and patient health by the investigators and by the patients for the SAF was predominantly "very good" or "good" at every end of year documentation (SAF). **Safety/Tolerability** Overall, 913 AEs were reported in 59 (73.8%) patients in the SAF. Of these, 893 AEs occurred in 52 (72.2%) patients of the "Severe" subgroup and only 20 AEs in 7 (87.5%) patients of the "Non-severe" subgroup. The majority of the 913 AEs was mild (666 AEs in 50 [62.5%] patients), followed by 173 moderate AEs in 34 (42.5%) patients and 28 severe AEs in 17 (21.3%) patients. The vast majority of the 913 AEs had the outcome "recovered/resolved" (814 AEs in 54 [67.5%] patients). None of the AEs were judged by the investigators to be related to Haemoctin SDH. In total, 52 SAEs in 23 (28.8%) patients were reported. Of these, 47 SAEs occurred in 20 (27.8%) patients of the "Severe" subgroup and 5 SAEs in 3 (37.5%) patients of the "Non-severe" subgroup. Overall, 756 AESIs (i.e., bleedings) were reported in 48 (60.0%) patients. Of these, 747 AESIs occurred in 44 (61.1%) patients of the "Severe" subgroup and 9 AESIs in 4 (50.0%) patients of the "Non-severe" subgroup. Overall, 4 AEs of the category of thromboembolic events were reported in 4 (5.0%) patients and 10 AEs of the category of hypersensitivity / anaphylactic reactions were reported in 8 (10%) patients. In the total SAF, no AEs of the categories of development of anti-FVIII inhibitor or transmission of infective agents were experienced by the patients. 4 AEs in 1 (1.3%) patient of the SAF resulted in death. The 4 fatal AEs were judged by the investigator not to be related to Haemoctin SDH. 4 AEs in 4 (5.0%) patients of the SAF led to discontinuation of Haemoctin SDH. The 4 AEs leading to discontinuation of Haemoctin SDH were judged by the investigators not to be related to Haemoctin SDH.

	In the PSAF population, safety results were very similar, primarily due to patient profile overlaps, and no significant divergent outcomes were observed. Overall, Haemoctin SDH was well tolerated and no new and formerly unknown information with regard to the safety of Haemoctin SDH became apparent in this study.
Discussion	The study limitations included a high rate of premature study termination: In the SAF, 58 (72.5%) patients did not complete the study but terminated prematurely. Moreover, different sizes of subgroups of the SAF, e.g., for hemophilia status (“Severe”, N=72; “Non-severe”, N=8) or treatment regimen (“Prophylaxis overall”, N=75; “on demand”, N=3) impaired a meaningful comparison of subgroups. Patients documented in this NIS at 11 German and 7 Hungarian hemophilia centers and 1 Austrian hemophilia center (with 2 sub-centers, i.e., children and adults) can be regarded as representative for hemophilia A patients living in the EU. The assessments of treatment effectiveness, tolerance and handling of Haemoctin SDH by the investigators and by the patients for the SAF was predominantly “very good” or “good” at every end of year documentation. Likewise, the investigators’ and patients’ assessment of patient health in the SAF was predominantly “very good” or “good” at every visit. Overall, treatment with Haemoctin SDH was well tolerated. No new and formerly unknown information with regard to the safety and tolerability of Haemoctin was reported during the study period. No AEs were judged to be related to Haemoctin SDH. Formation of FVIII inhibitors was not observed during the entire study. The study results confirm the positive benefit-risk profile of Haemoctin in the indication and prophylaxis of bleeding in patients with hemophilia A. The benefit-risk profile of Haemoctin remains clearly favorable.
Marketing Authorization Holder	Biotest AG Landsteinerstr. 5 63303 Dreieich, Germany

4. LIST OF ABBREVIATIONS

ABR	Annual bleeding rate
ADR	Adverse drug reaction
AE	Adverse event
AESI	Adverse event of special interest
AMS	AMS Advanced Medical Services GmbH (CRO)
APS	All patients set
ATC	Anatomic Therapeutic Chemical Classification System
BL	Baseline
BU	Bethesda units
BW	Body weight
CI	Confidence interval
CRA	Clinical research associate
CRO	Contract research organization
CSR	Clinical study report
DRM	Data review meeting
eCRF	electronic Case report form
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
EQ-5D	European Quality of Life 5 Dimensions
EQ-5D-Y	European Quality of Life 5 Dimensions-Youth
FAS	Full analysis set
FFP	Fresh frozen plasma
FPFV	First patient first visit
FVIII	Factor VIII
HEAD-US	Hemophilia early arthropathy detection with ultrasound
HIV	Human immunodeficiency virus
ICF	Informed consent form
ICH	Intracranial hemorrhage
IEC	Independent ethics committee
ITI	Immune tolerance induction
IU	International units
LPLV	Last patient last visit
MAH	Marketing authorization holder
MedDRA	Medical dictionary for regulatory activities
n	Number of patients with event / within category

N	Number in analysis population
NIS	Non-interventional study
PFAS	Pooled full analysis set
PSAF	Pooled safety analysis set
PT	Preferred term
PTP	Previously treated patients
PUP	Previously untreated patients
PV	Pharmacovigilance
QoL	Quality of life
SADR	Serious adverse drug reactions
SAE	Serious adverse events
SAESI	Serious adverse events of special interest
SAF	Safety analysis set
SAP	Statistical analysis plan
SAS	Statistical Analysis Software
SD	Standard deviation
SMQ	Standardized MedDRA Query
SOC	System organ class
SmPC	Summary of product characteristics
VAS	Visual analogue scale
WHO	World Health Organization
WHO DD	World Health Organization drug dictionary

5. INVESTIGATORS / HEALTH CARE PROFESSIONALS

See Appendix 1.4 (Section 17.1) of this report (List of stand-alone documents) for study sites in Germany, Hungary and Austria.

6. OTHER RESPONSIBLE PARTIES

Not applicable.

7. MILESTONES

Milestone	Planned date	Actual date	Comments
Start of data collection	Oct-2016	Oct-2016	Start of clinical phase (initiation of first study site)
End of data collection	Mar-2023	31-Dec-2022	
Registration in the ENCePP register	-	08-Jun-2016	EU PAS Register Number: EUPAS13728
Final report of study results	Dec-2023	08-Dec-2023	

8. RATIONALE AND BACKGROUND

8.1 Hemophilia A and the Treatment of Hemophilia A

Hemophilia A is an inherited, chronic bleeding disorder and is treated lifelong with factor VIII (FVIII) concentrates. Two treatment regimens are applied, on demand treatment and as prophylaxis. Most children and adolescents are treated prophylactically to prevent bleeding in industrialized countries. For patients who have started prophylaxis in childhood, this treatment is extended into adulthood. Prophylaxis has the goal to prevent bleeds, avoid permanent joint damage and ensure a high quality of life (QoL). Prophylactic treatment consists of regular FVIII applications, usually three times a week.

Development of neutralizing antibodies against FVIII (FVIII inhibitor) is the most significant complication of hemophilia care today. Antibodies inactivate the procoagulant activity of FVIII and inhibit patients' response to replacement therapy. As inhibitors tend to develop early in the course of FVIII treatment, the main challenge consists in avoiding inhibitors in this critical early phase of FVIII exposure as the subsequent risk is much lower [1].

Once developed, however, attempts for immune tolerance induction (ITI) have been successful, particularly with plasmatic factor preparations such as Haemoctin SDH [2].

8.2 Haemoctin SDH

Haemoctin SDH is a FVIII preparation derived from human plasma purified by chromatography. Haemoctin SDH is approved for prevention and treatment of congenital and acquired FVIII deficiencies. Details are given in the summary of product characteristics (SmPC) / German “Fachinformation” of Haemoctin SDH. Clinical efficacy, safety and pharmacokinetic properties of Haemoctin SDH were evaluated in three prospective open-label uncontrolled studies in previously treated patients (PTP) with severe hemophilia A. In conclusion, Haemoctin SDH has shown to be effective, safe and well tolerated for long-term prophylaxis, on demand treatment, as well as for pre- and post-operative use in minor and major surgical procedures [3].

Data on successfully performed ITI with Haemoctin SDH have been collected in patients with hemophilia A who have developed inhibitors to FVIII.

The stabilization of the FVIII molecule is carried out by the natural carrier protein von Willebrand factor. There is no need for the addition of auxiliary stabilizers such as sucrose or human serum albumin. It seems that FVIII preparations with von Willebrand factor will generate fewer inhibitors than products without von Willebrand factor [4].

In a previous non-interventional study (NIS) [5], data were obtained from patients treated with Haemoctin SDH over 18 years (1998 to 2015); these data can be extended in part with this new study. In the previous NIS, long-term effectiveness, safety and tolerability were investigated in 198 hemophilia A patients treated for prophylaxis or on demand, as required. Most patients were PTPs (168) and 30 patients were previously untreated patients (PUPs). The mean (±standard deviation [SD]) documentation time was 7.3±5.1 years per patient. A total of 1,418 patient-years were documented. The proportion of patients receiving treatment for prophylaxis increased from 41.1% (37/90 patients) in 2003 to 65.7% (44/67 patients) in 2015. The mean (±SD) Haemoctin exposure dose was 31.6±15.2 IU/kg body weight (BW).

Median annual bleeding rate (ABR) was considerably lower for patients treated prophylactically with Haemoctin SDH (3.1; range: 0.0-30.5) than patients treated on demand (21.9; range 0.0-113.3). Overall median ABR decreased over time (1998 to 2002: 20.7; 2008 to 2012: 5.2; 2013 to 2015: 2.6). The expected therapeutic effect was assessed by the investigators as “successful” for 99.4% of treatments. During the 18-year study period, 7 patients experienced 10 adverse events (AEs) that were related to study medication. All of them developed FVIII inhibitors. In conclusion, Haemoctin SDH was effective, safe and well tolerated in long-term prophylaxis and treatment on demand.

With the present long-term study, the documentation of some patients was extended and new patients were included. The primary focus was moved from safety to effectiveness and patient-reported QoL.

9. RESEARCH QUESTION AND OBJECTIVES

With this NIS long-term data under real life conditions in an international study population were generated.

9.1 Primary Objective

- Annual bleeding rate (ABR) defined as episodes per year in patients with Haemoctin SDH treatment, differentiated by prophylaxis and on demand treatment

$$ABR = \frac{\sum Bleeding\ episodes\ in\ the\ corresponding\ observation\ phase \times 365{,}25\ [Days/Year]}{\sum Duration\ of\ the\ corresponding\ observation\ phase\ [Days]}$$

9.2 Secondary Objectives

- Adverse events (AEs) and subsequent suspected adverse drug reactions (ADRs: AEs assessed by the investigator as being causally related to Haemoctin SDH treatment)
- AEs with bleeding = AEs of special interest (AESIs) with extended bleeding documentation, for example if the duration and severity of the bleeding corresponded to the situation, i.e., was expected or unexpected
- Occurrence and characterization of FVIII inhibitors to Haemoctin SDH
- QoL determined with the Euroqol EQ-5D in adults and the EQ-5D-Y in adolescents

10. AMENDMENTS AND UPDATES

The initial observation plan (version 1.0) was dated 28-Jan-2016. A self-standing local amendment 1.0 for the University Heidelberg was dated 18-Jul-2017. Version 2.0 of the observation plan was dated 18-Feb-2021.

Number	Date	Section of observation plan	Amendment or update
1 (local)	18-Jul-2017	Section 10	Extension of the description of the protection of human patients
2	18-Feb-2021	Abstract, Section 6, Section 9.2 Section 10	New time lines Extension of the description of the protection of human patients

11. RESEARCH METHODS

11.1 Study Design

This was a non-interventional, retrospective and prospective, single-arm, uncontrolled, multi-center, international, post marketing authorization study.

Haemoctin SDH treatment-related information from patients with hemophilia A was collected under routine treatment conditions in Germany, Hungary and Austria.

Collection of data partly relied on web-based patient documentations (smart medication) and/or on paper-based patient diaries. Further data were obtained from the patient files and during patient visits that were scheduled solely according to center-specific routine practice. Parameters outside the clinical routine were not collected.

11.2 Setting

Patients were treated at home and in some exceptional cases in a clinic or a local doctor's practice in Germany, Hungary and Austria.

Data collection was planned to begin in March 2016. An inclusion period of 7 years was planned. The end of the NIS was defined as either the last documentation performed in March 2023 or when 150 patients have been documented for at least 1 year.

The individual documentation per patient after start of treatment aimed for a documentation of at least 1 year.

Treatment-related data recorded by the investigator since inclusion in the NIS were documented in an electronic case report form (eCRF) and were included in the evaluation.

11.3 Patients

This NIS was performed in patients with hemophilia A.

Only patients meeting all of the following **inclusion criteria** were considered for the inclusion into the NIS:

- Treatment in accordance with the SmPC of Haemoctin SDH
- Children of all ages and adult patients with FVIII deficiency (including previously treated and previously untreated patients)
- Written informed consent to allow data collection and data transfer to third party

Patients meeting the following **exclusion criterion** were excluded from this NIS:

- Contraindications as provided in the SmPC

11.4 Variables

The following variables were planned to be collected or computed according to the observation plan and statistical analysis plan (SAP):

- Patient demographics (age, sex, ethnicity, body height and weight)
- Family history in relation to bleeding disorders, diagnosis (time of determination of hemophilia, date of first bleeding, baseline clotting factor activity, familiarity, mutation type), previous treatment of hemophilia, accompanying diseases
- Treatment (intended regimens: prophylaxis or on demand, total number of exposures per year, mean dose per kg per patient/year, total dose/year, batch number of Haemoctin SDH)
- The ABR in patients with Haemoctin SDH prophylaxis or on demand treatment (defined as the number of bleeding episodes per year in patients with Haemoctin SDH treatments reported during end of year follow-up visit)
- Number and severity of bleedings dependent on the treatment regime (prophylaxis or on demand) with the bleeding score [6]
- Patient-reported quality of life (QoL) determined with the questionnaires Euroqol EQ-5D in adults and EQ-5D-Y in adolescents (assessed at start of documentation, 3 months and 1 year after the start of the study and then annually) including absolute overall EQ-5D scores, the individual domain scores and the visual analogue scale (VAS) scores as well as change to baseline
- Occurrence of inhibitors to Haemoctin SDH with regard to the treatment regime (prophylaxis and on demand treatment), considering titers ≥0.6 BU (Bethesda units) as of clinically significant [7-9]
- Immunological characterization of antibodies against FVIII (antibody isotopes, subclasses and -binding sites) at study start and in case of FVIII inhibitor formation (to be analyzed by in the laboratory of the coordinating investigator as a sub-study analysis)
- In case of FVIII inhibitor formation clinical signs like hematoma formation, the FVIII trough levels
- The occurrence of adverse events (AEs), seriousness, severity, relationship to Haemoctin SDH treatment (related or not related) and outcome of the AE
- Adverse events of special interest (AESIs): Bleeding episodes in general and of high relevance (all major bleeds, e.g., gastrointestinal bleeds, joint bleeds or intracranial hemorrhage, bleeds with unexpected course or severity in context of the underlying situation) as well as FVIII inhibitor development. In addition, the analysis includes:
    - Thromboembolic events (Standardized MedDRA Query [SMQ] narrow: Embolic and thrombotic events)
    - Hypersensitivity / Anaphylactic reactions (SMQs broad: Hypersensitivity; Anaphylactic reaction)
    - Development of anti-FVIII inhibitors (Medical dictionary for regulatory activities [MedDRA] preferred terms [PTs]: Anti-FVIII antibody positive, anti-factor FVIII antibody test, and FVIII inhibition)

- Transmission of infective agents (MedDRA PTs: Transmission of infectious agent via product, Suspected Transmission of infectious agent via product)

- Laboratory values (hemoglobin, platelets, inhibitors, blood glucose), absolute values and annual changes from baseline
- Joint status (overall joint status and impact of affected joints on daily life by annual visit; number and percentage of patients with affected joints by location)
- Overall assessment by the patient and investigator of treatment effectiveness, tolerance and handling of Haemoctin SDH
- Assessment of patient's health condition evaluated by the investigator (documented by each regular follow-up visit)
- Activity of the person and days of illness / sick leave (e.g., not at work or school) due to hemophilia
- Reasons for stopping the documentation
- Optional, arthropathy progress assessed with ultrasound and quantified with the hemophilia early arthropathy detection with ultrasound (HEAD-US) score [10]

11.5 Data Sources and Measurement

Information on Haemoctin SDH treatment and the occurrence of bleedings were obtained from patient diaries either web-based (smart medication™) or paper-based. Further information was obtained from the patient files and during patient visits. Patient data were entered and stored in an electronic case report form (eCRF). AEs occurring in the course of the study had to be evaluated by the investigator and documented in the AE log of the eCRF.

Data on AEs were transferred to the clinical database by the contract research organization (CRO) and all data on AEs were forwarded to the drug safety department of the sponsor, either electronically via AE log or paper based via fax, for further processing of these data in Biotest's global pharmacovigilance database system. In the following report, the term 'Biotest's global pharmacovigilance database system' will be abbreviated as 'global PV database' throughout.

11.6 Bias

The limitations of the NIS were those typical of a NIS. Since the focus was to obtain clinical data from routine treatment, there was no control group and only routine clinical data could be obtained. Accordingly, it was not possible to guarantee documentation of all data defined in the observational plan and to document the data according to a fixed schedule such as in an interventional clinical study.

In addition, because the data were collected from various sources, as described in Section 11.5, and the majority of patients were treated at home, there was a delay in data transfer that presumably contributed to decreased accuracy of the data. For all these

reasons, i.e., the limitations associated with the observational nature of the study, home/self-treatment of the patients and the different means for the documentation of safety related information combined with certain lag times, exact matching datasets could not be guaranteed.

11.7 Study Size

As hemophilia is a rare disease, a formal sample size calculation was not applicable because the study population was restricted by the number of available patients receiving Haemoctin SDH treatment.

11.8 Data Transformation

Data were entered into the eCRF at the study site. Data entries were checked by automatic and manual queries according to a data validation plan. Corrections had to be entered into the eCRF at the study site. Questionnaires for quality of life were handed over to the patients by the clinical staff. After completion of the questionnaires, data had to be entered into the eCRF by the study site personal.

Individual information from the patients on their treatment (application of Haemoctin SDH with units, time of application, batch number), the occurrence and location of bleedings and whether associated with pain, swelling and restriction of motion were collected by the use of the app smart medication™ or from paper diaries. The choice of electronic or paper-based data collection was at the discretion of the patient and investigator. The smart medication app was used in those study centers where this technique was available and the patients were using it. Paper diaries were copied and forwarded to the CRO for data entry into the study data base. Furthermore, all data on AEs were also forwarded to the drug safety department of the sponsor, either electronically via AE log or paper-based via fax, for further processing of these data in the global PV database.

The final data were transferred to Statistical Analysis Software (SAS) for subsequent data analyses in accordance with the statistical analysis plan.

Coding

Concomitant medication was coded with the World Health Organization drug dictionary (WHO DD) 2022Sep01, which was the most recent version at the time of the analysis. AEs, previous and concomitant diseases were coded using MedDRA, both in the clinical database and global PV database. While version 25.1 was used in the clinical database, version 26.0 was used in the global PV database. In the clinical database, coding was done precisely according to the reported verbatim, whereas in the global PV database, significant emphasis was placed on capturing the exact medical context based on additional information provided or obtained.

Baseline Values

Values for laboratory parameters, physical examination, joint status, HEAD-US score, quality of life questionnaires and sick leave days collected at the baseline visit/first study visit were defined as the baseline values for these parameters.

If more than one valid value was available for a given variable before start of treatment (e.g., for a laboratory parameter), the chronologically last valid value was referred to as baseline value and was used for statistical summaries as well as change from baseline calculations.

Measurements taken during the baseline visit were assumed to have been taken “before start of treatment” even if the measurement was taken on study Day 1.

Data Review Meeting

Prior to database hard lock for the final analysis, a Data Review Meeting (DRM) was held on 14-Mar-2023, based on the database export of 06-Mar-2023. The main purpose of the DRM was to identify and resolve data issues that might impede meaningful interpretation of the study results and to redefine analyses as specified in the observation plan or SAP. DRM results are documented in the DRM minutes, version 1.0, dated 31-Mar-2023.

11.9 Statistical Methods

11.9.1 Main Summary Measures

Continuous (metric) variables were summarized by the number of observations n and number of missings, mean, standard deviation (SD), median, 25% and 75% percentiles, minimum, and maximum. Mean, median, quartiles were presented with one more significant decimal place than originally recorded in the data, SD with one more significant decimal place than originally recorded in the data, minimum and maximum values with the same number of decimal places as the original data. Where appropriate, change to baseline analyses were used to evaluate changes in values over follow-up time. Unless stated otherwise, the calculation of percentages was based on the total number of patients in the population of interest. Accordingly, counts of missing observations were included in the denominator and presented as a separate category.

Categorical (qualitative) variables were reported with absolute and relative frequencies (n, %). Percentages were rounded to one decimal place. Where appropriate, two-sided 95% confidence limits and descriptive p-values were reported.

11.9.2 Main Statistical Methods

All analyses were performed in an exploratory sense. Since no confirmatory analyses were planned, no hypotheses were formulated. Data were analyzed using descriptive statistics.

All analyses were performed using SAS Version 9.4 TS1M5.

The ABR and proportions of patients with an inhibitor formation per year were presented as percentages (total: size of Full Data Set) together with exact (according Pearson-Clopper) 2-sided upper 95%-confidence limits.

Analysis Populations

The following populations were defined:

1. **All Patients Set (APS):** This was the group of patients who have provided informed consent and for whom any data were captured in the study (noted as Full Data Set in the observation plan).
2. **Safety Analysis Set (SAF):** The group of all patients who received at least one dose of study medication. This population was used for the analysis of safety and tolerability data.
3. **Full Analysis Set (FAS):** This set was defined as all patients who received at least one dose of study medication during the course of the study and for whom at least one primary endpoint assessment (number of joint bleeds per year, as documented for the annual end of year visits on the eCRF page *Bleeding score*, variable *score.joint*) after baseline was available.
4. **Pooled full analysis set (PFAS):** This set was defined as all patients who received at least one dose of study medication during the course of this study ("Biotest NIS-016") and the previous study "Biotest NIS-013" and for whom at least one primary endpoint assessment after baseline was available.

Subgroup Analysis

The following subgroups were evaluated in this study:

- Country: Germany, Austria and Hungary
- Treatment regimen:
  i. Patients on prophylaxis overall
  ii. Patients on prophylaxis <20 IU / 3 times per week
  iii. Patients on prophylaxis ≥20 IU / 3 times per week
  iv. Patients with on demand treatment
- Previously untreated patients (PUPs) and previously treated patients (PTPs)
- Hemophilia status at baseline: Severe / non-severe hemophilia status based on baseline FVIII residual activity (severe hemophilia [FVIII activity ≤1%]; non-severe [FVIII activity >1%])

Safety

All safety analyses were based on the SAF and PSAF.

Safety and tolerability in this study were addressed and analyzed by the frequency, severity, seriousness and causality of adverse events (AEs). AEs, serious adverse events (SAEs), adverse drug reactions (ADRs) and serious adverse drug reactions (SADRs) were

presented separately in summary tables by MedDRA “system organ class” (SOC) and “preferred term” (PT) for each hemophilia status (severe / non-severe) and overall. These were also repeated by treatment regimen. Additionally, the number and percentage of injections with at least one ADR to the injection was determined.

As outlined in Section 11.5, two separate systems were utilized for capturing data on AEs, the clinical database and the global PV database. In order to present the data and analyses, i.e., seriousness and causality assessment, exactly as the investigators and site staff entered them into the eCRF, AEs from the clinical database were used to compile the respective tables and listings. Where appropriate, the terms used by the sponsor following their assessment of the medical context and analyses were added and compared.

FVIII inhibitors with titers ≥0.6 BU were analyzed with respect to clinical relevance for the patient (e.g., more bleeding, higher dosages).

11.9.3 Missing Values

All available data were included in the analyses and were summarized as far as possible.

Unless otherwise specified, there was no imputation of missing data, i.e., missing data were not replaced.

11.9.4 Sensitivity Analyses

Initially not planned; see Section 11.9.5.

11.9.5 Changes in the Planned Analyses

11.9.5.1 Sensitivity Analyses and Main Populations Analyzed

The yearly assessment of the number of joint bleeds (eCRF page *Bleeding score*, variable *score.joint*) provided the only mandatory documentation of bleedings, which also included the reporting of the non-occurrence of events and was therefore used to calculate the ABR (note: ABR covers the following analyses: 1. number and frequency of patients with bleedings, 2. number of bleedings and 3. annualized bleeding rate). By definition, the presence of at least one assessment was a prerequisite for inclusion in the FAS. However, an unexpectedly high number of 15 SAF patients did not have a primary endpoint assessment. Consequently, analyses planned to be conducted for the FAS covered only 76.2% of the enrolled patient population (APS). In order to include available data from non-FAS patients and not underestimate the ABR, the following sensitivity analyses were carried out:

Calculation of the Extended ABR as a Sensitivity Analysis

In order to calculate an ABR for non-FAS patients, an extended ABR Sensitivity Analysis was conducted.

In the course of the study, bleeding information was documented in several eCRF instruments and outside the eCRF:

- **Joint-Bleeds** (filled in by the investigator in the eCRF only at "end of year" visits). Note: This information was used for the ABR based on joint score assessment, which is only available for FAS patients.
- **Bleeding Page** (filled in by the investigator in the eCRF if bleeding occurred - independently of a visit)
- **Bleeding documentation** (filled in by the patient when bleedings occurred and transferred to the eCRF by the CRO - independently of a visit)
- **Diaries** (filled in by the patient outside the eCRF): Bleedings in connection with Haemoctin SDH administration was recorded (e.g., reason for administration = bleeding)

For the extended ABR sensitivity analysis bleeding information from the Bleeding Page and Bleeding documentation were used. Diaries were not considered for analysis as the documentation was inconsistent and any bleeding in the diaries should also be recorded on the Bleeding Page/documentation.

All events of a patient from the Bleeding Page and documentation were included in the analysis, regardless of bleed characteristics. For a patient with multiple bleedings on the same date, each bleeding was counted as a single event only if recorded for a different location. For a patient with multiple bleedings on the same date on both instruments, only the event from the Bleeding Page was counted as it was assumed to be the same event recorded twice. If no bleeding was documented for a patient and study year, it was assumed the patient did not have an event (= 0).

The calculation of the extended ABR was conducted as described in the SAP and was carried out on the FAS and SAF.

Additional Sensitivity Analyses on the SAF Originally Planned on the FAS

The following analyses, initially planned for the FAS, were additionally carried out for the SAF:

- Table 14.2.1.3 Treatment regimen
- Table 14.4.1.4.1.3 Number and severity of bleedings
- Table 14.4.1.4.2.3 Number and percentage of bleedings by location
- Table 14.4.2.2 Quality of Life
- Table 14.6.5.3 Assessment of treatment effectiveness, tolerance and handling of Haemoctin SDH by the investigator
- Table 14.6.6.3 Assessment of treatment effectiveness, tolerance and handling of Haemoctin SDH by the patient
- Table 14.6.7.2 Assessment of patient health by the investigator
- Figure 14.8.4: Assessment of treatment effectiveness, tolerance and handling of Haemoctin SDH

The results based on the SAF are considered the main results and are presented in this report. The ABR based joint score assessment and bleeding score tables were not carried out on the SAF as these would show the same results as for the FAS.

Change of Pooled Analysis Population from PFAS to PSAF

Originally, the pooled analysis population PFAS included only patients who were included in the FAS. Due to the low patient numbers in the FAS, the Pooled Analysis Population was extended to include patients in the SAF instead. Accordingly, the extended pooled analysis population was named Pooled Safety Analysis Set (PSAF). This increased the pooled population from 35 to 48 patients. All analyses initially planned for the PFAS were performed on the PSAF population. The corresponding results presented in this report are based on the PSAF population.

11.10 Quality Control

NIS Initiation Activities

The investigator(s) were informed about objectives and methods of the NIS by a Clinical Research Associate (CRA) from the CRO. This occurred after a signed contract with the study site, competent authority information and ethic commission approvals had been obtained. No documentations were supposed to be done before the site was trained at the initiation visit.

Electronic Case Report Form (eCRF)

All data to be recorded according to the NIS observation plan had to be documented in the eCRF. The investigator was instructed on how to use the eCRF for data entering. Entries in the eCRF had to be made only by the investigator or persons authorized by the investigator. An individual account for each authorized person was created. The investigator had to verify that all data entries in the eCRF were accurate and correct.

Quality Assurance

The quality of data and adherence to the NIS documentation plan, to legal and ethical requirements according to local laws were checked by Biotest, the CRO or a delegate from the CRO. A combination of centralized (automatic eCRF and manual checks) and on-site checks were applied to assure data quality in this NIS.

NIS source data verification was part of the quality assurance process and the investigator had to grant direct access to the NIS patients' source data. For this NIS at least one quality assurance (i.e., on-site monitoring) visit per site was planned to check the data entered. However, in 3 study sites that included patients, no monitoring visit could actually be performed. In addition, regular phone contacts were planned to resolve questions regarding data entry in the eCRF.

Audits and Inspections

Audits were to be performed according to the corresponding audit program, including the possibility that a member of the sponsor's quality assurance department might have arranged to visit the investigator in order to audit the performance of the NIS at the clinical site as well as all documents originating there. Audits might have also been performed by contract auditors. In this case, the sponsor's quality assurance department would have had to agree with the contract auditor regarding the timing and extent of the audit(s). In case of audits at the investigational site, a representative from the CRO would usually accompany the auditor(s).

Inspections by regulatory authority representatives and independent ethics committees (IECs) were possible at any time, even after the end of the NIS. The investigators and institutions had to permit NIS related quality assurance, audits, reviews by the ethics committee and/or regulatory authorities, and to allow direct access to source data and source documents for quality assurance, audits, and inspections.

In fact, no audits or inspections took place.

Archiving

After evaluation and reporting of the data, all documents relating to the NIS will be transferred to the sponsor and kept in the archives of sponsor for at least 10 years according to national and European law and the clinical sites according to applicable local regulatory requirements.

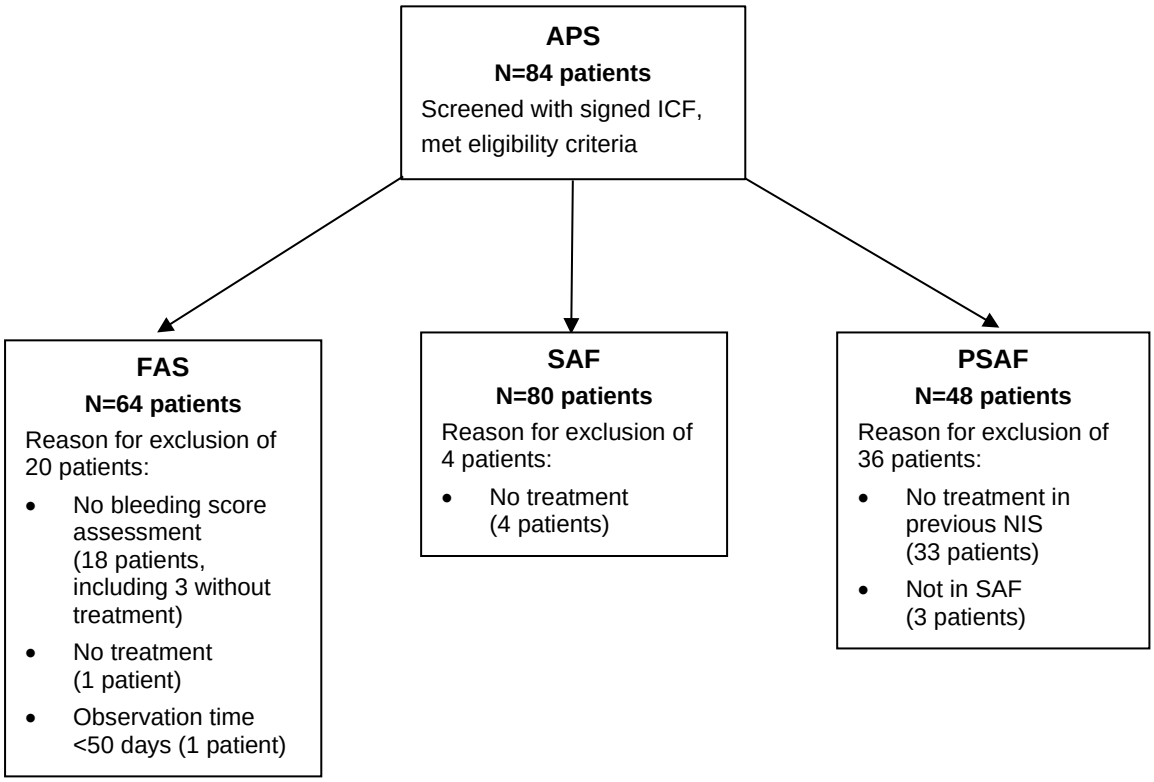
12. RESULTS

Statistical analysis tables can be found in Section 17.1 Appendix 1.5-1.7 (List of stand-alone documents).

12.1 Participants

Overall, 84 patients were enrolled in this NIS. They comprise the APS (named Full Data Set in the observation plan). Four patients were not treated with Haemoctin SDH (i.e., no corresponding entry in the diary, no previous treatment and no evidence for treatment in AE reports) and therefore excluded from all analyses. Figure 1 displays the patient flow based on the decisions of the DRM and, with respect to the PSAF, changes described in Section 11.9.5.

Figure 1 Disposition of patients



Source: Appendix Table 14.1.1

APS = All Patients Set, FAS = Full Analysis Set, ICF = Informed Consent Form, N = Number of patients in analysis population, NIS = Non-interventional Study, PSAF = Pooled Safety Analysis Set, SAF = Safety Analysis Set.

For the definition of analysis populations see Section 11.9.2, except for PSAF, which is defined in Section 11.9.5.1. Only one reason for exclusion is stated per excluded patient; however, there may have been more than one reason (for details per patient see Appendix Listing 16.2.2).

In the APS (N=84), 41 (48.8%) patients were recruited in Germany, 37 (44.0%) patients in Hungary and 6 (7.1%) patients in Austria. Of the 84 patients, 51 patients participated in the previous NIS (Biotest NIS-013), while 33 patients were newly included (Table 1). For more detail, including SAF and FAS, see Table 1.

Table 1 Number of patients in analysis populations by previous NIS participation and country (APS)

Total/Country	Analysis set	Participation in previous NIS (N=51)		No participation in previous NIS (N=33)		APS (N=84)	
		n	%	n	%	n	%
Total	APS	51	100.0	33	100.0	84	100.0
	SAF	48	94.1	32	97.0	80	95.2
	FAS	40	78.4	24	72.7	64	76.2
Germany	APS	16	31.4	25	75.8	41	48.8
	SAF	15	29.4	24	72.7	39	46.4
	FAS	8	15.7	16	48.5	24	28.6
Hungary	APS	35	68.6	2	6.1	37	44.0
	SAF	33	64.7	2	6.1	35	41.7
	FAS	32	62.7	2	6.1	34	40.5
Austria	APS	0	0.0	6	18.2	6	7.1
	SAF	0	0.0	6	18.2	6	7.1
	FAS	0	0.0	6	18.2	6	7.1

Source: Appendix Table 14.1.5

APS = All Patients Set, FAS = Full Analysis Set, N = number in analysis population, n = number of patients with event / in category, NIS = non-interventional study, SAF = Safety Analysis Set.

Participation in the previous NIS corresponds to documentation on eCRF instrument “NIS History”.

12.1.1 Premature Study Termination and Main Reasons

Within the APS, 61 (72.6%) patients terminated the study prematurely. The most common reason by far was “Patient switched to different FVIII product (plasma product)” in 37 (60.7%) patients, followed by “Patient switched to different FVIII product (recombinant product)” in 11 (18.0%) patients. All other main reasons were given only for 0 to 4 patients. All main reasons for premature study termination in the SAF, FAS and APS are shown in Table 2.

Table 2 Main reason for premature study termination (SAF, FAS, APS)

	SAF (N=80)		FAS (N=64)		APS (N=84)	
	n	%	n	%	n	%
Number of patients with premature study termination	58	72.5	44	68.8	61	72.6
Main reasons for termination:						
Patient switched to different FVIII product (plasma product)	35	60.3	34	77.3	37	60.7
Patient switched to different FVIII product (recombinant product)	11	19.0	6	13.6	11	18.0
Patient switched to different FVIII product (other treatment or treatment/product unknown)*	4	6.9	3	6.8	4	6.6
Insufficient patient cooperation	2	3.4	0	0.0	3	4.9
Patient lost to follow-up	2	3.4	0	0.0	2	3.3
(Serious) Adverse Event	1	1.7	1	2.3	1	1.6
Intercurrent disease	1	1.7	0	0.0	1	1.6
Patient deceased	1	1.7	0	0.0	1	1.6
No reason given	1	1.7	0	0.0	1	1.6

Source: Appendix Table 14.1.2

APS = All Patients Set, FAS = Full Analysis Set, FVIII = factor VIII, N = number in analysis population, n = number of patients with event / within category, SAF = Safety Analysis Set.

* Combined numbers for "Patient switched to different FVIII product (other treatment)", i.e., in the eCRF "Patient switched to different FVIII product" and "Other treatment" were selected, and "Patient switched to different FVIII product (treatment/product unknown)", i.e., in the eCRF "Patient switched to different FVIII product" and nothing else was selected.

12.1.2 Duration of Study: First Patient First Visit to Last Patient Last Visit

In the present study (Biotest NIS-016), first patient first visit (FPFV) to last patient last visit (LPLV) was 30-Nov-2016 to 05-Dec-2022 both in the APS (N=84) and in the SAF (N=80) (Appendix Tables 14.1.3.1-2). When combining data of the present study (Biotest NIS-016) and the previous study (Biotest NIS-013), FPFV to LPLV was 04-Nov-1998 to 05-Dec-2022 both in the APS (N=84) and in the SAF (N=80), including previous NIS patients not participating in the present study (Appendix Tables 14.1.4.1-2). The total observation time of the previous study with Haemoctin combined with the present study covers a period of up to about 24 years and enabled unique long-term data to be obtained from several patients.

12.2 Descriptive Data

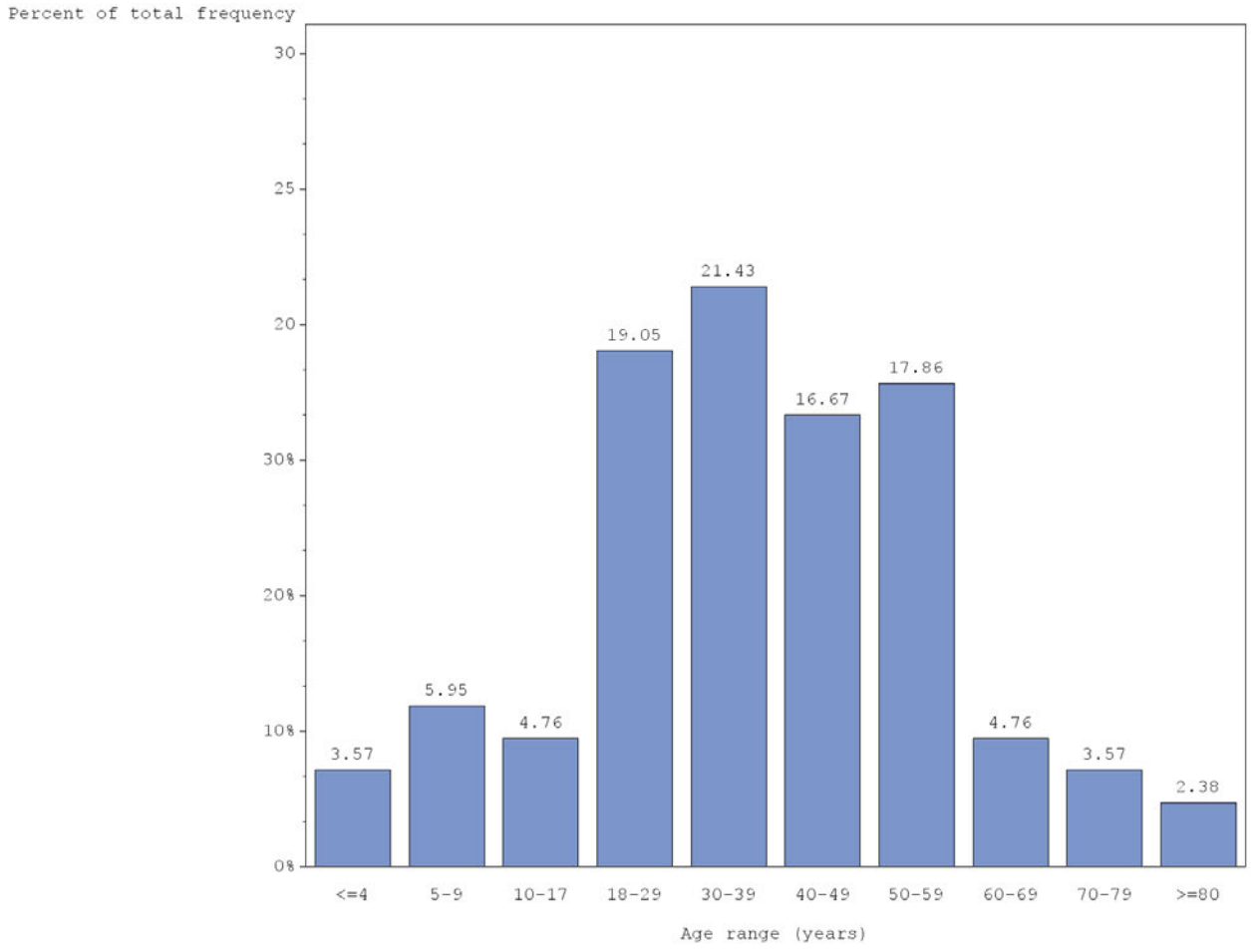
12.2.1 Demographics

At baseline, the patients of the total SAF (N=80) had a median age of 38.0 years, ranging from 2 to 81 years. Similarly, patients with severe hemophilia (N=72) had a median age of 38.5 years, ranging from 2 to 80 years. The smaller subgroup of patients with non-severe hemophilia (N=8) had a lower median age of 24.0 years, ranging from 18 to 81 years (Table 3).

In the APS, the largest group of patients (21%) belonged into the category 30 to 39 years (Figure 2). The age distribution in the SAF was similar to the APS shown in Figure 2; 1 out of 4 patients of the APS who were not included in the SAF belonged to the age category “5-9 years”, 1 patient belonged to the category “30-39 years” and 2 patients belonged to the category “40-49 years” (Appendix Listings 16.2.2 and 16.2.3).

All patients included in the SAF were male, as expected due to the gender-specific prevalence of hemophilia A. The predominant ethnicity was Caucasian (95.0% in the total SAF) (Table 3).

Figure 2 Age distribution at study inclusion for all patients (APS)



Source: Appendix Figure 14.8.1
APS = All Patients Set.

Further demographic data for the SAF, including body weight and height, are shown in Table 3.

Table 3 Demographic data by hemophilia status (severe vs non-severe) at baseline (SAF)

Characteristics	Statistics	Hemophilia status		
		Severe (N=72)	Non-severe (N=8)	Total (N=80)
Age [years]	n (missing)	72 (0)	8 (0)	80 (0)
	Mean (SD)	38.4 (18.8)	35.1 (22.4)	38.1 (19.1)
	Median	38.5	24.0	38.0
	Min - Max	2 - 80	18 - 81	2 - 81
Body weight [kg]	n (missing)	71 (1)	8 (0)	79 (1)
	Mean (SD)	73.0 (22.7)	83.1 (11.3)	74.0 (22.0)
	Median	75.0	80.5	75.0
	Min - Max	9 - 110	72 - 107	9 - 110
Body height [cm]	n (missing)	66 (6)	8 (0)	74 (6)
	Mean (SD)	168.3 (24.5)	178.1 (6.8)	169.4 (23.5)
	Median	174.5	178.5	175.0
	Min - Max	74 - 196	169 - 188	74 - 196
Gender	n (missing)	72 (0)	8 (0)	80 (0)
male		72 (100.0%)	8 (100.0%)	80 (100.0%)
Ethnicity	n (missing)	72 (0)	8 (0)	80 (0)
Caucasian		68 (94.4%)	8 (100.0%)	76 (95.0%)
Asian		1 (1.4%)	0 (0.0%)	1 (1.3%)
Other		3 (4.2%)	0 (0.0%)	3 (3.8%)

Source: Appendix Tables 14.1.6.1, 14.1.7.1

N = number in analysis population, n = number of patients with event / in category, SAF = Safety Analysis Set, SD = standard deviation.

12.2.2 Family History

For 36 patients in the SAF, cases of hemophilia A in the family were recorded. The affected family members were the brother for 24 (70.6%) patients, the uncle for 7 (20.6%) patients and the grandfather for 3 (8.8%) patients (data missing for 2 patients; Table 4).

FVIII inhibitors in family members were not present for 20 (57.1%) patients but present for 7 (20.0%) patients. Presence was not known for 8 (22.9%) patients (data missing for 1 patient; Table 4).

Table 4 Family history of hemophilia A (SAF)

Characteristics	Total (N=80)
Patients with cases of hemophilia A in the family	36 (100.0%)
Family relation affected with hemophilia A*	
Brother	24 (70.6%)
Uncle	7 (20.6%)
Grandfather	3 (8.8%)
Missing	2 (-)
Presence of FVIII inhibitors in family members	
Yes	7 (20.0%)
No	20 (57.1%)
not known	8 (22.9%)
Missing	1 (-)

Source: Appendix Tables 14.1.8.1

FVIII = factor VIII, N = number in analysis population, SAF = Safety Analysis Set.

* Multiple answers were possible (but did not occur).

Percentages refer to patients with non-missing data.

12.2.3 Disease History

12.2.3.1 Hemophilia A History

In the SAF (N=80), the median age at diagnosis of hemophilia A was 1.0 year (range 0 to 70 years) and the median time since hemophilia A diagnosis at baseline was 35.5 years (range 0 to 75 years). Similarly, in the subgroup of patients with severe hemophilia A (N=72), the median age at diagnosis of hemophilia A was 1.0 year (range 0 to 70 years) and median time since hemophilia A diagnosis was 38.0 years (range 0 to 75 years). In the smaller subgroup of patients with non-severe hemophilia A (N=8), the median age at diagnosis of hemophilia A was 4.0 years (range 1 to 12 years) and median time since hemophilia A diagnosis was 18.0 years (range 17 to 69 years) (Table 5).

Median baseline FVIII residual activity at baseline was 1.0% of normal (range 0 to 24%) for the total SAF, 0.5% (range 0 to 1%) for the subgroup of patients with severe hemophilia A and 4.5% (range 1 to 24%) for the subgroup of patients with non-severe hemophilia A (Table 5).

The majority of patients (>90% in total and both subgroups) had no other hemostatic disorder (not examined in 2.5% of all patients). The majority of patients (>70% in total and both subgroups) had no thrombophilia (not examined in 20% of all patients) (Table 5).

Table 5 Hemophilia A history of patients by hemophilia status at baseline (SAF)

Characteristics	Statistics	Hemophilia status		
		Severe (N=72)	Non-severe (N=8)	Total (N=80)
Age at diagnosis of hemophilia A [years]	n (missing)	59 (13)	5 (3)	64 (16)
	Mean (SD)	3.4 (10.7)	5.2 (4.4)	3.6 (10.3)
	Median	1.0	4.0	1.0
	Min - Max	0 - 70	1 - 12	0 - 70
Time since hemophilia A diagnosis [years]	n (missing)	59 (13)	5 (3)	64 (16)
	Mean (SD)	35.7 (18.0)	30.2 (22.4)	35.3 (18.2)
	Median	38.0	18.0	35.5
	Min - Max	0 - 75	17 - 69	0 - 75
Baseline FVIII residual activity [%]	n (missing)	72 (0)	8 (0)	80 (0)
	Mean (SD)	0.5 (0.5)	8.2 (8.3)	1.3 (3.4)
	Median	0.5	4.5	1.0
	Min - Max	0 - 1	1 - 24	0 - 24
Presence of another hemostatic disorder				
Yes		3 (4.2%)		3 (3.8%)
No		67 (93.1%)	8 (100.0%)	75 (93.8%)
Not examined		2 (2.8%)		2 (2.5%)
Presence of thrombophilia				
Yes		3 (4.2%)		3 (3.8%)
No		53 (73.6%)	8 (100.0%)	61 (76.3%)
Not examined		16 (22.2%)		16 (20.0%)

Source: Appendix Table 14.1.9.1

FVIII = factor VIII, N = number in analysis population, n = number of patients with event / in category, SAF = Safety Analysis Set, SD = standard deviation.

12.2.3.2 Inhibitor History

At baseline, FVIII inhibitors were present in 8 (10%) patients of the total SAF, 7 (9.7%) patients of the “Severe” subgroup and 1 (12.5%) patient of the “Non-severe” subgroup. FVIII inhibitors were not present in all remaining patients (Table 6).

The median time since detection of FVIII inhibitors in the SAF was 10 years (range 1 to 43 years). The median age at first exposure to any blood product in the SAF was 0.9 years (range 0 to 42 years). The median age at first exposure to any factor concentrates in the SAF was 13 years (range 0 to 70 years) (Table 6).

Table 6 Inhibitor history by hemophilia status at baseline (SAF)

Characteristics	Statistics	Hemophilia status		
		Severe (N=72)	Non-severe (N=8)	Total (N=80)
Presence of FVIII inhibitor at the beginning of the NIS				
Yes	n (%)	7 (9.7%)	1 (12.5%)	8 (10.0%)
No	n (%)	65 (90.3%)	7 (87.5%)	72 (90.0%)
Method used for detection of FVIII inhibitors				
Bethesda	n (%)	4 (66.7%)	1 (100.0%)	5 (71.4%)
Nijmegen	n (%)	2 (33.3%)		2 (28.6%)
No inhibitor or missing information	n (%)	66 (-)	7 (-)	73 (-)
Additional blood products at the time of inhibitor occurrence				
Yes	n (%)	2 (33.3%)		2 (33.3%)
No	n (%)	4 (66.7%)		4 (66.7%)
No blood product or missing information	n (%)	66 (-)	8 (-)	74 (-)
Type of additional blood products at the time of inhibitor occurrence				
Blood	n (%)	1 (50.0%)		1 (50.0%)
FFP	n (%)	1 (50.0%)		1 (50.0%)
No additional blood products or missing information	n (%)	70 (-)	8 (-)	78 (-)
Treatment regimen practiced at inhibitor occurrence				
On demand	n (%)	3 (50.0%)	1 (100.0%)	4 (57.1%)
Prophylaxis	n (%)	3 (50.0%)		3 (42.9%)
No inhibitor or missing information	n (%)	66 (-)	7 (-)	73 (-)
Years since detection of FVIII inhibitors	n (missing*)	7 (65)	1 (7)	8 (72)
	Mean (SD)	14 (15)	18 (.)	14 (14)
	Median	8	18	10
	Min - Max	1 - 43	18 - 18	1 - 43
Age at first exposure to any blood product [years]	n (missing*)	35 (37)	2 (6)	37 (43)
	Mean (SD)	4.0 (9.0)	3.5 (3.6)	3.9 (8.8)
	Median	0.9	3.5	0.9
	Min - Max	0 - 42	1 - 6	0 - 42
Age at first exposure to any factor concentrates [years]	n (missing*)	37 (35)	3 (5)	40 (40)
	Mean (SD)	15.8 (16.9)	8.6 (9.3)	15.3 (16.5)
	Median	15.0	6.0	13.0
	Min - Max	0 - 70	1 - 19	0 - 70

Source: Appendix Table 14.1.10.1

FFP = fresh frozen plasma, FVIII = factor VIII, N = number in analysis population, n = number of patients with event / in category, NIS = non-interventional study, SAF = Safety Analysis Set, SD = standard deviation.

* ”Missing” includes patients without any inhibitor or blood product.

Percentages refer to patients with non-missing data.

12.2.3.3 Previous Treatment for Hemophilia A

In the total SAF, 65 patients (corresponding to 100% of patients) had previous treatment for hemophilia A (Table 7).

Among predefined reasons for the decision for treatment with Haemoctin (multiple answers possible), “no particular reason” was recorded for 26 (40.0%) patients, “efficacy” for 20 (30.8%) patients, “initiation of immune tolerance therapy” for 19 (29.2%) patients and “better recovery” for 17 (26.2%) patients. Further reasons were recorded for less than 20% of patients (Table 7).

The treatment regimen at the time of being enrolled in the NIS was “prophylactic” for the majority of patients (54 patients, 83.1%), “on demand” for 9 (13.8%) patients and “undefined” for 2 (3.1%) patients (Table 7).

The type of prophylaxis was most frequently “tertiary prophylaxis with existing arthropathy” (26 patients, 40.0%), followed by “secondary prophylaxis after the first bleed” (22 patients, 33.8%), “undefined” (11 patients, 16.9%) and “primary prophylaxis before the first bleed” (6 patients, 9.2%) (Table 7).

The median FVIII dosage was 2000 IU (range 13 to 4000 IU). The median number of supplementations per week were 3 (range 1 to 14). The median target trough level was 2% (range 1 to 120%) (Table 7).

Table 7 Previous treatment for hemophilia A (SAF)

Characteristics	Statistics	Total (N=80)
Patients with previous treatment	n (%)	65 (100.0%)
Reasons for decision for treatment with Haemoctin*		
No particular reason	n (%)	26 (40.0%)
Efficacy	n (%)	20 (30.8%)
Initiation of immune tolerance therapy	n (%)	19 (29.2%)
Better recovery	n (%)	17 (26.2%)
Pharmaceutical drug safety	n (%)	10 (15.4%)
Previous medication no longer available	n (%)	10 (15.4%)
Better packaging sizes	n (%)	8 (12.3%)
Other reasons	n (%)	8 (12.3%)
Treatment regimen at the time of being enrolled in the NIS		
Prophylactic treatment	n (%)	54 (83.1%)
On demand treatment	n (%)	9 (13.8%)
Undefined	n (%)	2 (3.1%)
Type of prophylaxis		
Primary prophylaxis before the first bleed	n (%)	6 (9.2%)
Secondary prophylaxis after the first bleed	n (%)	22 (33.8%)
Tertiary prophylaxis with existing arthropathy	n (%)	26 (40.0%)
Undefined	n (%)	11 (16.9%)
FVIII dosage [IU]	n (missing)	54 (11)
	Mean (SD)	2038.1 (1063.8)
	Median	2000.0
	Min - Max	13 - 4000
Number of supplementations per week	n (missing)	40 (25)
	Mean (SD)	3.2 (2.1)
	Median	3.0
	Min - Max	1 - 14**
Target trough level [%]	n (missing)	41 (24)
	Mean (SD)	9.0 (21.4)
	Median	2.0
	Min - Max	1 - 120

Source: Appendix Table 14.1.11.1

FVIII = factor VIII, IU= international units, N = number in analysis population, n = number of patients with event / in category, NIS = non-interventional study, SAF = Safety Analysis Set, SD = standard deviation.

* Multiple answers possible.

** The indicated maximum of 14 treatments per week corresponds to the actual documentation for one patient. The patient had an inhibitor history (Appendix Listing 16.2.5), the reason for the decision for treatment with Haemoctin was “Other reasons: Positive effect regarding the FVIII inhibitor” (Appendix Listing 16.2.7) and the patient received prophylactic treatment with 3000 IU daily (Appendix Listings 16.2.5, 16.2.7). Although immune tolerance therapy is not explicitly documented for this patient, the frequent administration of Haemoctin is therefore probably related to immune tolerance therapy.

12.2.3.4 Infection Status

At study entry chronic hepatitis B infection was recorded for 3 (3.8%) patients and a Human Immunodeficiency Virus (HIV) infection was recorded for 1 (1.3%) patient (Appendix Table 14.1.12.1).

12.2.4 Concomitant Diseases

In the SAF, 36 (45.0%) patients had at least one concomitant disease (Table 8).

The three most frequent system organ classes were “musculoskeletal and connective tissue disorders” (26 patients, 32.5%), “vascular disorders” (16 patients, 20.0%) and “infections and infestations” (15 patients, 18.8%). The four most frequent preferred terms were “haemophilic arthropathy” (19 patients, 23.8%), “hypertension” (16 patients, 20.0%), “chronic hepatitis c” and “hepatitis c” (both in 6 patients, 7.5%) (Table 8).

Table 8 Concomitant diseases in ≥2% of patients (SAF)

SYSTEM ORGAN CLASS preferred term	Total (N=80)	
	n*	%
Patients with at least one disease	36	45.0
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	26	32.5
haemophilic arthropathy	19	23.8
arthritis	2	2.5
arthropathy	2	2.5
back pain	2	2.5
VASCULAR DISORDERS	16	20.0
hypertension	16	20.0
INFECTIONS AND INFESTATIONS	15	18.8
chronic hepatitis c	6	7.5
hepatitis c	6	7.5
hepatitis b	4	5.0
GASTROINTESTINAL DISORDERS	8	10.0
chronic gastritis	3	3.8
gastrooesophageal reflux disease	2	2.5
haemorrhoids	2	2.5
METABOLISM AND NUTRITION DISORDERS	7	8.8
hypercholesterolaemia	3	3.8
RENAL AND URINARY DISORDERS	6	7.5
chronic kidney disease	2	2.5
ENDOCRINE DISORDERS	4	5.0
hypothyroidism	2	2.5
HEPATOBILIARY DISORDERS	4	5.0
liver disorder	3	3.8
SURGICAL AND MEDICAL PROCEDURES	4	5.0
knee arthroplasty	4	5.0
antiviral treatment	2	2.5
NERVOUS SYSTEM DISORDERS	3	3.8
REPRODUCTIVE SYSTEM AND BREAST DISORDERS	3	3.8
benign prostatic hyperplasia	3	3.8
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	3	3.8
EYE DISORDERS	2	2.5
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	2	2.5
PSYCHIATRIC DISORDERS	2	2.5
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	2	2.5

Source: Appendix Table 14.1.13.1

MedDRA = Medical Dictionary for Regulatory Activities, N = number in analysis population, SAF = Safety Analysis Set.

* As patients could have more than one concomitant disease, n for the system organ class can be smaller than the sum of all n of the associated preferred terms. Furthermore, due to the cut-off (≥2% of patients), all preferred terms that were documented for only one patient are not shown in this table.

Diseases were coded using MedDRA version 25.1.

12.3 Outcome Data

As described in Section 11.9.5, most analyses were based on the SAF, either as initially planned or – if the initial plan according to the SAP was to use the FAS – as sensitivity analyses. The corresponding results are regarded the main results of this study and are primarily presented in this report. However, analysis of ABR (Section 12.4.4.2) and bleeding score (indicating number and severity of bleedings; Section 12.4.7) were carried out only on the FAS as originally planned and not repeated on the SAF as these would show the same results as for the FAS comprising all patients for whom at least one primary endpoint assessment (i.e., pertaining to the ABR, bleeding score assessment) after baseline was available.

The SAF included 80 patients and comprised the two subgroups of patients with severe hemophilia A (N=72) and with non-severe hemophilia A (N=8).

The pooled analysis population for the combined analysis of results from the previous (Biotest NIS-013) and the current study (Biotest NIS-016) was the PSAF (see Section 11.9.5).

The PSAF included 48 patients who participated in both studies and were therefore observed for a longer time (Section 12.1.2).

12.4 Main Results

12.4.1 Treatment Regimens

In the SAF including all countries, the predominant treatment regimen was prophylaxis, namely for 75 (93.8%) patients in total (N=80), 71 (98.6%) patients in the “Severe” subgroup (N=72) and 4 (50.0%) patients in the smaller “Non-severe” subgroup (N=8) (Table 9). Only a minority of patients received on demand treatment, namely 3 (3.8%) patients in total, 1 (1.4%) patient in the “Severe” subgroup and 2 (25.0%) patients in the “Non-severe” subgroup. Data on the treatment regimen were missing for the remaining 2 patients; they belonged to the “Non-severe” subgroup in Germany (Appendix Listing 16.2.2).

Among the 75 patients in the SAF who received prophylactic treatment, 26 (32.5%) patients received “≥20 IU/kg 3 times per week”, 14 (17.5%) received “<20 IU/kg 3 times per week” and the remaining 35 patients (33 in the “Severe” subgroup and 2 in the “Non-severe” subgroup) did not receive one of these two specific prophylaxis regimens (Table 9; Appendix Listing 16.2.2). The frequency of injections per week for patients receiving prophylactic treatment, including regimens not mentioned above, is shown in Table 12.

The predominant use of Haemoctin SDH for prophylactic treatment was also observed in the individual participating countries, Germany, Hungary and Austria. In Germany, 35/39 patients received prophylactic treatment and 2/39 patients on demand treatment (data on regimen missing for 2 patients; Appendix Listing 16.2.2). In Hungary,

34/35 patients received prophylactic treatment and 1/35 patients on demand treatment. In Austria, all 6 patients received prophylactic treatment (Table 9).

The specific prophylactic regimens were more frequently used in Germany and Austria than in Hungary. In Germany, 15/35 patients with prophylaxis received prophylactic regimen "≥20 IU/kg 3 times per week", 11/35 patients received "<20 IU/kg 3 times per week", while for 9/35 patients no prophylactic regimen was specified (Table 9).

Patients with non-severe hemophilia A were included only in Germany and their number was low (N=8; data on regimen missing for 2 patients). Nevertheless, treatment regimens by country and by severity status are presented in Table 9.

Table 9 Treatment regimens overall and by country (SAF)

Characteristics	Hemophilia status					
	Severe (N=72)		Non-severe (N=8)		Total (N=80)	
	n	%	n	%	n	%
Treatment regimens: All countries						
Prophylaxis	71	98.6	4	50.0	75	93.8
<20 IU/kg 3 times per week	12	16.7	2	25.0	14	17.5
≥20 IU/kg 3 times per week	26	36.1			26	32.5
On demand	1	1.4	2	25.0	3	3.8
Treatment regimens: Germany						
Prophylaxis	31	43.1	4	50.0	35	43.8
<20 IU/kg 3 times per week	9	12.5	2	25.0	11	13.8
≥20 IU/kg 3 times per week	15	20.8			15	18.8
On demand			2	25.0	2	2.5
Treatment regimens: Hungary						
Prophylaxis	34	47.2			34	42.5
<20 IU/kg 3 times per week	1	1.4			1	1.3
≥20 IU/kg 3 times per week	7	9.7			7	8.8
On demand	1	1.4			1	1.3
Treatment regimens: Austria						
Prophylaxis	6	8.3			6	7.5
<20 IU/kg 3 times per week	2	2.8			2	2.5
≥20 IU/kg 3 times per week	4	5.6			4	5.0

Source: Appendix Table 14.2.1.3

IU = international units, N = number in analysis population, n = number of patients with event / in category, SAF = Safety Analysis Set.

Similar to the SAF, in the PSAF (N=48) the predominant treatment regimen was prophylaxis, namely for 47 (97.9%) patients (Table 10). Only 1 (2.1%) patient received on demand treatment; this patient was included in Hungary. As in the previous NIS (Biotest NIS-013) only German and Hungarian sites participated, Austrian patients are not part of the PSAF.

Treatment regimens for the FAS are shown in Appendix Table 14.2.1.1 but not presented here because the FAS is not considered the main analysis population in this report (see Section 11.9.5).

Table 10 Treatment regimens overall and by country (PSAF)

Characteristics	Hemophilia status					
	Severe (N=47)		Non-severe (N=1)		Total (N=48)	
	n	%	n	%	n	%
Treatment regimen: All countries						
Prophylaxis	46	97.9	1	100.0	47	97.9
<20 IU/kg 3 times per week	5	10.6	1	100.0	6	12.5
≥20 IU/kg 3 times per week	12	25.5			12	25.0
On demand	1	2.1			1	2.1
Treatment regimen: Germany						
Prophylaxis	14	29.8	1	100.0	15	31.3
<20 IU/kg 3 times per week	5	10.6	1	100.0	6	12.5
≥20 IU/kg 3 times per week	5	10.6			5	10.4
Treatment regimen: Hungary						
Prophylaxis	32	68.1			32	66.7
≥20 IU/kg 3 times per week	7	14.9			7	14.6
On demand	1	2.1			1	2.1

Source: Appendix Table 14.2.1.2

N = number in analysis population, n = number of patients with event / in category, PSAF = Pooled Safety Analysis Set.

12.4.2 Exposure to Study Medication

In the SAF, the median number of exposures per year were 128.5 (range 1 to 155; data for 17 patients missing) in Germany, 142.8 (range 5 to 344; data for 25 patients missing) in Hungary and 159.7 (range 117 to 219) in Austria (Table 11).

The median total dose per year was 190189 IU/year (range 1459 to 458686 IU/year; data for 18 patients missing) in Germany, 435037 IU/year (range 188064 – 1030705 IU/year; data for 26 patients missing) in Hungary and 161056 IU/year (range 40601 – 438300 IU/year) in Austria (Table 11).

The total dose per year and kg body weight was 2759 IU/year/kg (range 18 - 5734 IU/year/kg; data for 18 patients missing) in Germany, 5417 IU/year/kg (range 1791 - 13091 IU/year/kg; data for 26 patients missing) in Hungary and 3442 IU/year/kg (range 2550 - 8117 IU/year/kg) in Austria (Table 11).

Exposure to study medication in subgroups by treatment regimen are shown in Appendix Table 14.2.2.1.1. The subgroup “Prophylaxis” (total N=75) is largely overlapping with and similar to the SAF. The number of patients in specific prophylaxis regimens is low (≤26 patients) so that a comparison to the SAF appears not meaningful.

Table 11 Exposure to study medication by country (SAF)

Parameter	Statistics	Hemophilia status		
		Severe (N=72)	Non-severe (N=8)	Total (N=80)
Number of exposures per year				
Germany	n (missing)	19 (12)	3 (5)	22 (17)
	Mean (SD)	118.4 (40.8)	45.5 (39.0)	108.4 (47.2)
	Median	135.5	31.2	128.5
	Min – Max	1 – 155	16 – 90	1 – 155
Hungary	n (missing)	10 (25)		10 (25)
	Mean (SD)	140.9 (87.5)		140.9 (87.5)
	Median	142.8		142.8
	Min – Max	5 – 344		5 – 344
Austria	n (missing)	6 (0)		6 (0)
	Mean (SD)	159.3 (36.5)		159.3 (36.5)
	Median	159.7		159.7
	Min - Max	117 - 219		117 - 219
Total dose/year [IU/year]				
Germany	n (missing)	19 (12)	2 (6)	21 (18)
	Mean (SD)	208685 (101848)	152084 (38518.5)	203295 (98487.7)
	Median	222397	152084	190189
	Min - Max	1459 - 458686	124847 - 179321	1459 - 458686
Hungary	n (missing)	9 (26)		9 (26)
	Mean (SD)	449921 (251537)		449921 (251537)
	Median	435037		435037
	Min - Max	188064 - 1030705		188064 - 1030705
Austria	n (missing)	6 (0)		6 (0)
	Mean (SD)	176166 (138747)		176166 (138747)
	Median	161056		161056
	Min - Max	40601 - 438300		40601 - 438300
Total dose/year/kg [IU/year/kg]				
Germany	n (missing)	19 (12)	2 (6)	21 (18)
	Mean (SD)	2891 (1349)	1575 (142.1)	2766 (1340)
	Median	2913	1575	2759
	Min - Max	18 - 5734	1475 - 1676	18 - 5734
Hungary	n (missing)	9 (26)		9 (26)
	Mean (SD)	5435 (3293)		5435 (3293)
	Median	5417		5417
	Min - Max	1791 - 13091		1791 - 13091
Austria	n (missing)	6 (0)		6 (0)
	Mean (SD)	4085 (2070)		4085 (2070)
	Median	3442		3442
	Min - Max	2550 - 8117		2550 - 8117

Source: Appendix Table 14.2.2.1

IU = international units, N = number in analysis population, n = number of patients with event / in category, SAF = Safety Analysis Set, SD = standard deviation.

Exposure period ranged from baseline to end of study.

The frequency of injections per week for patients on prophylaxis treatment in the SAF is shown separately for each treatment year in Table 12. In Year 1, the most common frequency of injections was “3 times a week” in 22 (29.3%) patients (data for 36 patients were missing). In the following years, “3 times a week” remained the most common frequency with 18 (24.0%) patients in Year 2 (data for 49 patients were missing), 16 (21.3%) patients in Year 3 (data for 50 patients were missing), 9 (12.0%) patients in Year 4 (data for 59 patients were missing) and 5 (6.7%) patients in Year 5 (data for 66 patients were missing). Frequencies are also shown separately for the “Severe” (N=71) and “Non-severe” (N=4) subgroup in Table 12.

Table 12 Frequency of injections (prophylaxis patients only) (SAF)

	Hemophilia status					
	Severe (N=71)		Non-severe (N=4)		Total (N=75)	
	n	%	n	%	n	%
Year 1						
1 time a week			1	25.0	1	1.3
2 times a week	9	12.7			9	12.0
3 times a week	21	29.6	1	25.0	22	29.3
3.5 times a week	3	4.2			3	4.0
7 times a week	3	4.2			3	4.0
14 times a week	1	1.4			1	1.3
Missing	34	47.9	2	50.0	36	48.0
Year 2						
2 times a week	5	7.0			5	6.7
3 times a week	17	23.9	1	25.0	18	24.0
3.5 times a week	3	4.2			3	4.0
Missing	46	64.8	3	75.0	49	65.3
Year 3						
2 times a week	4	5.6			4	5.3
3 times a week	16	22.5			16	21.3
3.5 times a week	3	4.2			3	4.0
7 times a week	2	2.8			2	2.7
Missing	46	64.8	4	100.0	50	66.7
Year 4						
2 times a week	3	4.2			3	4.0
3 times a week	9	12.7			9	12.0
3.5 times a week	4	5.6			4	5.3
Missing	55	77.5	4	100.0	59	78.7
Year 5						
2 times a week	3	4.2			3	4.0
3 times a week	5	7.0			5	6.7
3.5 times a week	1	1.4			1	1.3
Missing	62	87.3	4	100.0	66	88.0

Source: Appendix Table 14.2.3.1

N = number in analysis population, n = number of patients with event / in category, SAF = Safety Analysis Set.

Only patients on prophylaxis treatment were considered. Injection information was taken from eCRF entries only (no diaries).

Changes in the frequency of injections for each treatment year are presented in a shift table for all end of year documentations (Table 13). Changes in follow-up visits and changes in the subgroups “Severe” and “Non-severe” are shown in Appendix Table 14.2.4.1.

Overall, patient numbers were low and only few patients changed injection frequency. For example, in the end of year documentation of Year 1, which included 32 patients, 2 patients shifted from 1 to 2 times a week, 1 patient shifted from 2 to 3 times a week and 1 patient shifted from 3.5 to 7 times a week as compared with baseline. The remaining 28 patients did not change injection frequencies (Table 13).

Table 13 Shift table of change in frequency of injections (SAF)

Visit/Frequency	Baseline: Number of supplementations per week				
	1/week	2/week	3/week	3.5/week	7/week
Year 1, end of year documentation	2	6	19	4	1
2 times a week	2 (100.0%)	5 (83.3%)			
3 times a week		1 (16.7%)	19 (100.0%)		
3.5 times a week				3 (75.0%)	
7 times a week				1 (25.0%)	1 (100.0%)
Year 2, end of year documentation	2	6	15	3	
2 times a week	1 (50.0%)	4 (66.7%)			
3 times a week	1 (50.0%)	2 (33.3%)	15 (100.0%)		
3.5 times a week				3 (100.0%)	
Year 3, end of year documentation	2	6	13	3	
2 times a week	1 (50.0%)	3 (50.0%)			
3 times a week	1 (50.0%)	2 (33.3%)	12 (92.3%)		
3.5 times a week				3 (100.0%)	
7 times a week		1 (16.7%)	1 (7.7%)		
Year 4, end of year documentation	2	4	5	3	
2 times a week	1 (50.0%)	2 (50.0%)			
3 times a week	1 (50.0%)	2 (50.0%)	4 (80.0%)		
3.5 times a week			1 (20.0%)	3 (100.0%)	
Year 5, end of year documentation	1	3	2	1	
2 times a week	1 (100.0%)	1 (33.3%)			
3 times a week		2 (66.7%)	2 (100.0%)		
3.5 times a week				1 (100.0%)	

Source: Appendix Table 14.2.4.1

SAF = Safety Analysis Set.

Only patients on prophylaxis treatment were considered. Injection information was taken from eCRF entries only (no diaries).

12.4.3 Evaluation of the Treatment Course for Hemophilia A

An evaluation of the treatment course for hemophilia A in the SAF at the end of year documentation of Years 1 to 4 is shown in Table 14. The evaluation at follow-up visits – usually with lower patient numbers – is shown in Appendix Table 14.2.5.1. The end of year documentation of Year 5 does not contain any patient data.

In Year 1, 7 (8.8%) patients had a modification of their treatment regimen and 5 (6.3%) patients had danger signals. In Year 2, 4 (5.0%) patients had a modification of their treatment regimen and 4 (5.0%) patients had danger signals. In Year 3, 2 (2.5%) patients had a modification of their treatment regimen and 2 (2.5%) patients had danger signals. In Year 4, 3 (3.8%) patients had a modification of their treatment regimen and 1 (1.3%) patient had danger signals (Table 14). In hemophilia, the danger signal effect implies that endogenous or exogenous danger or damage signals present at the time of FVIII infusion stimulate the immune response. Danger signals include surgeries, bleedings and infections; for details per patient see Appendix Listing 16.2.7. Evaluation of the treatment course for subgroups by treatment regimen are shown in Appendix Table 14.2.5.1.1.

Table 14 Evaluation of the treatment course for hemophilia A (SAF)

Visit Characteristic	Hemophilia status Severe (N=72) n	 %	 Non-severe (N=8) n	 %	 Total (N=80) n	 %
YEAR 1, END OF YEAR DOCUMENTATION						
Patients with modification of treatment regimen	**7**	**9.7**	**0**	**0.0**	**7**	**8.8**
Treatment regimen modification:						
Begin of permanent prophylaxis with IU/kg body weight x/week	1	1.4	0	0.0	1	1.3
FVIII dosage change to IU/kg body weight	0	0.0	0	0.0	0	0.0
Prophylaxis interval change to supplementations/week	3	4.2	0	0.0	3	3.8
Trough target level change	1	1.4	0	0.0	1	1.3
Additional FVIII application due to bleeding	0	0.0	0	0.0	0	0.0
Intensified on demand therapy with individual prophylactic doses	0	0.0	0	0.0	0	0.0
Type of prophylaxis:						
Primary	1	1.4	0	0.0	1	1.3
Secondary	0	0.0	0	0.0	0	0.0
Patients with presence of danger signals	**4**	**5.6**	**1**	**12.5**	**5**	**6.3**
YEAR 2, END OF YEAR DOCUMENTATION						
Patients with modification of treatment regimen	**4**	**5.6**	**0**	**0.0**	**4**	**5.0**
Treatment regimen modification:						
FVIII dosage change to IU/kg body weight	1	1.4	0	0.0	1	1.3
Prophylaxis interval change to supplementations/week	2	2.8	0	0.0	2	2.5
Intensified on demand therapy with individual prophylactic doses	1	1.4	0	0.0	1	1.3
Patients with presence of danger signals	**4**	**5.6**	**0**	**0.0**	**4**	**5.0**
YEAR 3, END OF YEAR DOCUMENTATION						
Patients with modification of treatment regimen	**2**	**2.8**	**0**	**0.0**	**2**	**2.5**
Treatment regimen modification:						
FVIII dosage change to IU/kg body weight	1	1.4	0	0.0	1	1.3
Prophylaxis interval change to supplementations/week	1	1.4	0	0.0	1	1.3
Patients with presence of danger signals	**2**	**2.8**	**0**	**0.0**	**2**	**2.5**
YEAR 4, END OF YEAR DOCUMENTATION						
Patients with modification of treatment regimen	**3**	**4.2**	**0**	**0.0**	**3**	**3.8**
Treatment regimen modification:						
FVIII dosage change to IU/kg body weight	2	2.8	0	0.0	2	2.5
Additional FVIII application due to bleeding	1	1.4	0	0.0	1	1.3
Patients with presence of danger signals	**1**	**1.4**	**0**	**0.0**	**1**	**1.3**

Source: Appendix Table 14.2.5.1

FVIII = factor VIII, IU = international units, N = number in analysis population, n = number of patients with event / in category, SAF = Safety Analysis Set.

12.4.4 Annual Bleedings

Originally, analysis of annual bleedings and the ABR was planned to be solely based on the annual Joint Score Assessment. As described in Section 11.9.5, an extended analysis of bleeding events was calculated as sensitivity analysis, based on information from the Bleeding Page (filled in by the investigator in the eCRF) and the bleeding documentation

(filled in by the patient when bleedings occurred and transferred to the eCRF) (for details see Section 11.9.5). Here, the annual bleeding results according to the originally planned analysis are described first, followed by the extended annual bleeding results.

12.4.4.1 Annual Bleedings Based on the annual Joint Score Assessment

Data on overall annual bleedings based on the annual Joint Score Assessment in the FAS including subgroups by treatment regimen and previous treatment are shown in Table 15. The associated data on annual bleedings in each individual year of treatment are shown in Appendix Tables 14.3.1.1, 14.3.1.1.1, 14.3.1.1.2 for the FAS and Appendix Tables 14.3.1.2, 14.3.1.2.1, 14.3.1.2.2 for the PSAF. For the analysis of the PSAF, joint scores were not available in the former NIS; instead, all documented bleeding events were used, which limits the meaningfulness of the combined analysis. Consequently, for the PSAF only the extended annual bleedings based on the Bleeding Page are shown (Section 12.4.4.2).

Respective data for the SAF are shown in Appendix Tables 14.3.1.3, 14.3.1.3.1, 14.3.1.3.2. However, because a joint score is only available for FAS patients, the absolute numbers for SAF are the same as for FAS and are not described separately in this report.

In the total FAS, 64 patients had bleeding documentation and of these 32 (50%) patients had bleedings during the current study. The 95%-Clopper-Pearson confidence interval (CI) for the incidence rate was [37.23%; 62.77%]. A total of 382 bleeding events were documented (Table 15).

Compared with the total FAS, in the “Prophylaxis” subgroup of the FAS, the percentage of patients with bleedings was similar (50.82%). In the “Prophylaxis <20 IU/kg 3 times/week” subgroup of the FAS, the percentage of patients with bleedings was higher (75%) compared with the “Prophylaxis ≥20 IU/kg 3 times/week” subgroup with (47.37%). The percentage of PUPs with bleedings (50%) and PTPs with bleedings (52%) was similar (Table 15).

Table 15 Overall annual bleedings in the FAS and in subgroups by treatment regimen and previous treatment based on annual Joint Score Assessment (FAS)

(Sub)population: Annual bleedings, overall	Hemophilia status: Severe (N=59) n/N (%) - No. events	Severe (N=59) 95%-CI	Non-severe (N=5) n/N (%) - No. events	Non-severe (N=5) 95%-CI	Total (N=64) n/N (%) - No. events	Total (N=64) 95%-CI
FAS: Annual bleedings, overall	32/59 (54.24%) - 382	[40.75%; 67.28%]	0/5 (0.00%)	[0.00%; 52.18%]	32/64 (50.00%) - 382	[37.23%; 62.77%]
Subgroups by treatment regimen						
Prophylaxis: Annual bleedings, overall	31/58 (53.45%) - 366	[39.87%; 66.66%]	0/3 (0.00%)	[0.00%; 70.76%]	31/61 (50.82%) - 366	[37.70%; 63.86%]
Prophylaxis <20 IU/kg 3 times/week: Annual bleedings, overall	9/11 (81.82%) - 166	[48.22%; 97.72%]	0/1 (0.00%) - 0	[0.00%; 97.50%]	9/12 (75.00%) - 166	[42.81%; 94.51%]
Prophylaxis ≥20 IU/kg 3 times/week: Annual bleedings, overall	9/19 (47.37%) - 36	[24.45%; 71.14%]	No joint score available	-	9/19 (47.37%) - 36	[24.45%; 71.14%]
Subgroups by previous treatment						
PUPs: Annual bleedings, overall	6/10 (60.00%) - 33	[26.24%; 87.84%]	0/2 (0.00%) - 0	[0.00%; 84.19%]	6/12 (50.00%) - 33	[21.09%; 78.91%]
PTPs: Annual bleedings, overall	26/48 (54.17%) - 349	[39.17%; 68.63%]	0/2 (0.00%) - 0	[0.00%; 84.19%]	26/50 (52.00%) - 349	[37.42%; 66.34%]

Source: Appendix Tables 14.3.1.1, 14.3.1.1.1, 14.3.1.1.2

CI = confidence interval, FAS = Full Analysis Set, IU = international units, N = number in analysis population, n = number of patients with event / in category, No. = number, PTP = previously treated patient, PUP = previously untreated patient.

Results are presented in the following format: Number of patients with events / Number of patients (% of patients with events) - Number of events, where number of patients are the patients at the visit with bleeding documentation. 95%-CI is the 95%-Clopper-Pearson Confidence interval for incidence rate.

Previously (un)treated as documented at baseline on form “Prior and/or other treatment for hemophilia A (other than Haemoctin)”.

12.4.4.2 Annual Bleedings Based on the Bleeding Page

Data on overall annual bleedings based on the Bleeding Page in the FAS, PSAF and SAF including subgroups by treatment regimen and previous treatment are shown in Table 16, Table 17 and Table 18. The associated data on annual bleedings in each individual year of treatment are shown in Appendix Tables 14.3.1.1.b, 14.3.1.1.1.b, 14.3.1.1.2.b for the FAS, Appendix Tables 14.3.1.2.b, 14.3.1.2.1.b, 14.3.1.2.2.b for the PSAF and Tables 14.3.1.3.b, 14.3.1.3.1.b, 14.3.1.3.2.b for the SAF.

In the total FAS, 52 patients had bleedings during the current study and 64 patients had bleeding documentation. So, 81.25% of patients had bleedings. The 95%-Clopper-Pearson CI for the incidence rate was [69.54%; 89.92%]. A total of 987 bleeding events were documented (Table 16).

Compared with the total FAS, in the “Prophylaxis” subgroup of the FAS, the percentage of patients with bleedings was similar (81.97%). In the “Prophylaxis <20 IU/kg 3 times/week” subgroup of the FAS, the percentage of patients with bleedings was higher (100%) compared with the “Prophylaxis ≥20 IU/kg 3 times/week” subgroup (78.95%). The percentage of PUPs with bleedings (58.33%) was lower than the percentage of PTPs with bleedings (86.00%) (Table 16).

In the total PSAF, 47 patients had bleedings during the combined previous and current studies and 48 patients had bleeding documentation. So, 97.92% of patients had bleedings. A total of 17142 bleeding events was documented during this long-term observation. The 95%-Clopper-Pearson CI for the incidence rate was [88.93%; 99.95%] (Table 17).

Compared with the total PSAF, in the “Prophylaxis”, “Prophylaxis <20 IU/kg 3 times/week” and “Prophylaxis ≥20 IU/kg 3 times/week” subgroups the percentage of patients with bleedings was similar (97.87%, 100% and 91.67%). Also, the percentage of PUPs with bleedings (100%) and PTPs with bleedings (97.44%) was similar (Table 17).

In the total SAF, 61 patients had bleedings during the current studies and 80 patients had bleeding documentation. So, 76.25% of patients had bleedings. A total of 1126 bleeding events was documented. The 95%-Clopper-Pearson CI for the incidence rate was [65.42%; 85.05%] (Table 18).

Compared with the total SAF, in the “Prophylaxis” subgroup of the SAF, the percentage of patients with bleedings was similar (76.00%). In the “Prophylaxis <20 IU/kg 3 times/week” subgroup of the SAF, the percentage of patients with bleedings was higher (92.86%) compared with the “Prophylaxis ≥20 IU/kg 3 times/week” subgroup (65.38%). The percentage of PUPs with bleedings (53.85%) was lower than the percentage of PTPs with bleedings (80.00%) (Table 18).

Because the extended analyses include all types of bleedings and are not limited to joint bleeds (see analysis based on joint score assessment, Section 12.4.4.1), the number of percentages of patients with events and the number of events were higher for the extended analysis.

In the SAF the number of bleeding events tends to be higher than in the FAS, while the percentage of patients with bleeding tends to be lower than in the FAS.

Table 16 Overall annual bleedings in the FAS and in subgroups by treatment regimen and previous treatment based on the Bleeding Page (FAS)

(Sub)population: Annual bleedings, overall	Hemophilia status: Severe (N=59) n/N (%) - No. events	Severe (N=59) 95%-CI	Non-severe (N=5) n/N (%) - No. events	Non-severe (N=5) 95%-CI	Total (N=64) n/N (%) - No. events	Total (N=64) 95%-CI
FAS: Annual bleedings, overall	49/59 (83.05%) - 984	[71.03%; 91.56%]	3/5 (60.00%) - 3	[14.66%; 94.73%]	52/64 (81.25%) - 987	[69.54%; 89.92%]
Subgroups by treatment regimen						
Prophylaxis: Annual bleedings, overall	48/58 (82.76%) - 966	[70.57%; 91.41%]	2/3 (66.67%) - 2	[9.43%; 99.16%]	50/61 (81.97%) - 968	[70.02%; 90.64%]
Prophylaxis <20 IU/kg 3 times/week: Annual bleedings, overall	11/11 (100.00%) - 442	[71.51%; 100%]	1/1 (100.00%) - 1	[2.50%; 100%]	12/12 (100.00%) - 443	[73.54%; 100%]
Prophylaxis ≥20 IU/kg 3 times/week: Annual bleedings, overall	15/19 (78.95%) - 127	[54.43%; 93.95%]	No joint score available	-	15/19 (78.95%) - 127	[54.43%; 93.95%]
Subgroups by previous treatment						
PUPs: Annual bleedings, overall	6/10 (60.00%) - 73	[26.24%; 87.84%]	1/2 (50.00%) - 1	[1.26%; 98.74%]	7/12 (58.33%) - 74	[27.67%; 84.83%]
PTPs: Annual bleedings, overall	42/48 (87.50%) - 903	[74.75%; 95.27%]	1/2 (50.00%) - 1	[1.26%%; 98.74%]	43/50 (86.00%) - 904	[73.26%; 94.18%]

Source: Appendix Tables 14.3.1.1.b, 14.3.1.1.1.b, 14.3.1.1.2.b

CI = confidence interval, FAS = Full Analysis Set, IU = international units, N = number in analysis population, n = number of patients with event / in category, No. = number, PTP = previously treated patient, PUP = previously untreated patient.

Results are presented in the following format: Number of patients with events / Number of patients (% of patients with events) - Number of events, where number of patients are the patients at the visit with bleeding documentation. 95%-CI is the 95%-Clopper-Pearson Confidence interval for incidence rate.

Previously (un)treated as documented at baseline on form “Prior and/or other treatment for hemophilia A (other than Haemoctin)”.

Table 17 Overall annual bleedings in the PSAF and in subgroups by treatment regimen and previous treatment based on the Bleeding Page (PSAF)

(Sub)population: Annual bleedings, overall	Hemophilia status: Severe (N=47) n/N (%) - No. events	Severe (N=47) 95%-CI	Non-severe (N=1) n/N (%) - No. events	Non-severe (N=1) 95%-CI	Total (N=48) n/N (%) - No. events	Total (N=48) 95%-CI
PSAF: Annual bleedings, overall	46/47 (97.87%) - 17139	[88.71%; 99.95%]	1/1 (100.00%) - 3	[2.50%; 100%]	47/48 (97.92%) - 17142	[88.93%; 99.95%]
Subgroups by treatment regimen						
Prophylaxis: Annual bleedings, overall	45/46 (97.83%) - 17049	[88.47%; 99.94%]	1/1 (100.00%) - 3	[2.50%; 100%]	46/47 (97.87%) - 17052	[88.71%; 99.95%]
Prophylaxis <20 IU/kg 3 times/week: Annual bleedings, overall	5/5 (100.00%) - 712	[47.82%; 100%]	1/1 (100.00%) - 3	[2.50%; 100%]	6/6 (100.00%) - 715	[54.07%; 100%]
Prophylaxis ≥20 IU/kg 3 times/week: Annual bleedings, overall	11/12 (91.67%) - 2732	[61.52%; 99.79%]	No joint score available	-	11/12 (91.67%) - 2732	[61.52%; 99.79%]
Subgroups by previous treatment						
PUPs: Annual bleedings, overall	9/9 (100.00%) - 6773	[66.37%; 100%]	No joint score available	-	9/9 (100.00%) - 6773	[66.37%; 100%]
PTPs: Annual bleedings, overall	37/38 (97.37%) - 10366	[86.19%; 99.93%]	1/1 (100.00%) - 3	[2.50%; 100%]	38/39 (97.44%) - 10369	[86.52%; 99.94%]

Source: Appendix Tables 14.3.1.2.b, 14.3.1.2.1.b, 14.3.1.2.2.b

CI = confidence interval, IU = international units, N = number in analysis population, n = number of patients with event / in category, No. = number, PFAS = Pooled Full Analysis Set, PTP = previously treated patient, PUP = previously untreated patient.

Results are presented in the following format: Number of patients with events / Number of patients (% of patients with events) - Number of events, where number of patients are the patients at the visit with bleeding documentation. 95%-CI is the 95%-Clopper-Pearson Confidence interval for incidence rate.

Previously (un)treated as documented at baseline on form “Prior and/or other treatment for hemophilia A (other than Haemoctin)”.

Table 18 Overall annual bleedings in the SAF and in subgroups by treatment regimen and previous treatment based on the Bleeding Page (SAF)

(Sub)population: Annual bleedings, overall	Hemophilia status: Severe (N=72) n/N (%) - No. events	Severe (N=72) 95%-CI	Non-severe (N=8) n/N (%) - No. events	Non-severe (N=8) 95%-CI	Total (N=80) n/N (%) - No. events	Total (N=80) 95%-CI
SAF: Annual bleedings, overall	56/72 (77.78%) - 1116	[66.44%; 86.73%]	5/8 (62.50%) - 10	[24.49%; 91.48%]	61/80 (76.25%) - 1126	[65.42%; 85.05%]
Subgroups by treatment regimen						
Prophylaxis: Annual bleedings, overall	55/71 (77.46%) - 1098	[66.00%; 86.54%]	2/4 (50.00%) - 2	[6.76%; 93.24%]	57/75 (76.00%) - 1100	[64.75%; 85.11%]
Prophylaxis <20 IU/kg 3 times/week: Annual bleedings, overall	12/12 (100.00%) - 458	[73.54%; 100%]	1/2 (50.00%) - 1	[1.26%; 98.74%]	13/14 (92.86%) - 459	[66.13%; 99.82%]
Prophylaxis ≥20 IU/kg 3 times/week: Annual bleedings, overall	17/26 (65.38%) - 130	[24.45%; 71.14%]	No patients with bleedings	-	17/26 (65.38%) - 130	[44.33%; 82.79%]
Subgroups by previous treatment						
PUPs: Annual bleedings, overall	6/11 (54.55%) - 73	[23.38%; 83.25%]	1/2 (50.00%) - 1	[1.26%; 98.74%]	7/13 (53.85%) - 74	[25.13%; 80.78%]
PTPs: Annual bleedings, overall	49/60 (81.67%) - 1035	[69.56%; 90.48%]	3/5 (60.00%) - 8	[14.66%; 94.73%]	52/65 (80.00%) - 1043	[68.23%; 88.90%]

Source: Appendix Tables 14.3.1.3.b, 14.3.1.3.1.b, 14.3.1.3.2.b

CI = confidence interval, IU = international units, N = number in analysis population, n = number of patients with event / in category, No. = number, PTP = previously treated patient, PUP = previously untreated patient, SAF = Safety Analysis Set.

Results are presented in the following format: Number of patients with events / Number of patients (% of patients with events) - Number of events, where number of patients are the patients at the visit with bleeding documentation. 95%-CI is the 95%-Clopper-Pearson Confidence interval for incidence rate.

Previously (un)treated as documented at baseline on form “Prior and/or other treatment for hemophilia A (other than Haemoctin)”.

12.4.5 Annual Bleeding Rate

Evaluation of the ABR was the primary objective of this study. Only 1 out of 3 patients in the SAF with on demand treatment had a bleeding score assessment (and was therefore included in the FAS). Consequently, the ABR is only shown for prophylactic treatment but not for on demand treatment as initially planned by the primary objective.

Originally, analysis of the ABR was planned to be solely based on bleeding information from the Joint-Bleeds eCRF instrument. As described in Section 11.9.5, an extended ABR was calculated as sensitivity analysis, based on information from the Bleeding Page (filled in by the investigator in the eCRF) and the bleeding documentation (filled in by the patient when bleedings occurred and transferred to the eCRF) (for details see Section 11.9.5). Here, the ABR results according to the originally planned analysis are described first, followed by the extended ABR.

12.4.5.1 Annual Bleeding Rate Based on the Joint-Bleeds eCRF Instrument

Data on the overall ABR in the FAS including subgroups by treatment regimen and previous treatment are shown in Table 19. The associated data on the ABR in each individual year of treatment are shown in Appendix Tables 14.3.2.1, 14.3.2.1.1, 14.3.2.1.2 for the FAS and Appendix Tables 14.3.2.2, 14.3.2.2.1, 14.3.2.2.2 for the PSAF.

Respective data for the SAF are shown in Appendix Tables 14.3.2.3, 14.3.2.3.1, 14.3.2.3.2. However, as a joint score is only available for FAS patients and not for non-FAS SAF patients, only the FAS data and not the SAF data are described in this report.

In the total FAS, the median ABR was 0.12 (Table 19). The median ABR in the “Prophylaxis <20 IU/kg 3 times/week” subgroup was higher than in the “Prophylaxis ≥20 IU/kg 3 times/week” subgroup (2.47 vs. 0.0). The median ABR of PUPs and of PTPs was identical (0.24) (Table 19).

Table 19 Annual bleeding rate based on annual Joint Score Assessment in the FAS and in subgroups by treatment regimen and previous treatment (FAS)

(Sub)population: ABR, overall	Statistics	Hemophilia status Severe (N=59)	Non-severe (N=5)	Total (N=64)
FAS: ABR, overall	n (missing)	59 (0)	5 (0)	64 (0)
	Mean (SD)	1.57 (2.71)	0.00 (0.00)	1.45 (2.63)
	95% CI	0.86 - 2.27	0.00 - 0.00	0.79 - 2.10
	t-Test			<0.0001
	Median	0.29	0.00	0.12
	Min - Max	0.0 - 11.0	0.0 - 0.0	0.0 - 11.0
Subgroups by treatment regimen				
Prophylaxis: ABR, overall	n (missing)	58 (0)	3 (0)	61 (0)
	Mean (SD)	1.52 (2.71)	0.00 (0.00)	1.45 (2.66)
	95% CI	0.81 - 2.24	0.00 - 0.00	0.77 - 2.13
	t-Test			<0.0001
	Median	0.27	0.00	0.24
	Min - Max	0.0 - 11.0	0.0 - 0.0	0.0 - 11.0
Prophylaxis <20 IU/kg 3 times/week: ABR, overall	n (missing)	11 (0)	1 (0)	12 (0)
	Mean (SD)	3.19 (3.19)	0.00 (-)	2.93 (3.17)
	95% CI	1.05 - 5.33	(-)	0.91 - 4.94
	t-Test			-
	Median	3.36	0.00	2.47
	Min - Max	0.0 - 8.8	0.0 - 0.0	0.0 - 8.8
Prophylaxis ≥20 IU/kg 3 times/week: ABR, overall	n (missing)	19 (0)		19 (0)
	Mean (SD)	0.71 (1.73)		0.71 (1.73)
	95% CI	-0.12 - 1.55		-0.12 - 1.55
	Median	0.00		0.00
	Min - Max	0.0 - 7.4		0.0 - 7.4
Subgroups by previous treatment				
PUPs: ABR, overall	n (missing)	10 (0)	2 (0)	12 (0)
	Mean (SD)	0.85 (1.06)	0.00 (0.00)	0.71 (1.02)
	95% CI (t-Test)	0.09 - 1.61	0.00 - 0.00	0.06 - 1.35
	t-Test			0.0318
	Median	0.60	0.00	0.24
	Min - Max	0.0 - 3.3	0.0 - 0.0	0.0 - 3.3
PTPs: ABR, overall	n (missing)	48 (0)	2 (0)	50 (0)
	Mean (SD)	1.75 (2.94)	0.00 (0.00)	1.68 (2.90)
	95% CI (t-Test)	0.90 - 2.60	0.00 - 0.00	0.86 - 2.50
	t-Test			0.0001
	Median	0.27	0.00	0.24
	Min - Max	0.0 - 11.0	0.0 - 0.0	0.0 - 11.0

Source: Appendix Tables 14.3.2.1, 14.3.2.1.1, 14.3.2.1.2

ABR = annual bleeding rate, CI = confidence interval, FAS = Full Analysis Set, IU = international units, N = number in analysis population, n = number of patients with event / in category, PTP = previously treated patient, PUP = previously untreated patient, SD = standard deviation.

ABR = (number of bleeds at end of year visit*365.25)/patients annual observation time [days] based on patients at visit with bleeding documentation. Annual observation time = time between current and previous end of year visit. Overall observation time = sum of annual observation times.

The t-test compares the mean ABR between the severe and non-severe subgroups; however, the results are only shown if there were at least 2 observations per subgroup.

Previously (un)treated as documented at baseline on form “Prior and/or other treatment for hemophilia A (other than Haemoctin)”.

12.4.5.2 Extended Annual Bleeding Rate

Analysis of the extended ABR is based on the eCRF Bleeding Page and Bleeding documentation. Because non-joint bleedings were also documented on the Bleeding Page, the extended ABR results were expected to be generally higher than in the previously described analysis based on the Joint-Bleeds eCRF Instrument.

Data on the overall extended ABR in the FAS, PSAF and SAF including subgroups by treatment regimen and previous treatment are shown in Table 20, Table 21 and Table 22. The associated data on the ABR in each individual year of treatment are shown in Appendix Tables 14.3.2.1.b, 14.3.2.1.1.b, 14.3.2.1.2.b for the FAS, Appendix Tables 14.3.2.2.b, 14.3.2.2.1.b, 14.3.2.2.2.b for the PSAF and Appendix Tables 14.3.2.3.b, 14.3.2.3.1.b, 14.3.2.3.2.b for the SAF.

In the total FAS, the median extended ABR was 0.72 (Table 20). The median extended ABR in the “Prophylaxis <20 IU/kg 3 times/week” subgroup was higher than in the “Prophylaxis ≥20 IU/kg 3 times/week” subgroup (2.67 vs. 0.87). The median extended ABR of PUPs was lower than of PTPs (0.24 vs. 0.88) (Table 20).

Table 20 Extended annual bleeding rate based on Bleeding Page in the FAS and in subgroups by treatment regimen and previous treatment (FAS)

(Sub)population: Extended ABR, overall	Statistics	Hemophilia status: Severe (N=59)	Hemophilia status: Non-severe (N=5)	Total (N=64)
FAS: Extended ABR, overall	n (missing)	59 (0)	5 (0)	64 (0)
	Mean (SD)	4.36 (10.39)	0.00 (0.00)	4.02 (10.04)
	95% CI	1.65 - 7.07	0.00 - 0.00	1.51 - 6.53
	t-Test			0.0021
	Median	0.90	0.00	0.72
	Min - Max	0.0 - 60.3	0.0 - 0.0	0.0 - 60.3
Subgroups by treatment regimen				
Prophylaxis: Extended ABR, overall	n (missing)	58 (0)	3 (0)	61 (0)
	Mean (SD)	4.35 (10.48)	0.00 (0.00)	4.14 (10.26)
	95% CI	1.60 - 7.11	0.00 - 0.00	1.51 - 6.77
	t-Test			0.0025
	Median	0.88	0.00	0.72
	Min - Max	0.0 - 60.3	0.0 - 0.0	0.0 - 60.3
Prophylaxis <20 IU/kg 3 times/week: Extended ABR, overall	n (missing)	11 (0)	1 (0)	12 (0)
	Mean (SD)	9.61 (17.92)	0.00 (-)	8.81 (17.31)
	95% CI	-2.43 - 21.65	(-)	-2.19 - 19.81
	t-Test			-
	Median	3.75	0.00	2.67
	Min - Max	0.2 - 60.3	0.0 - 0.0	0.0 - 60.3
Prophylaxis ≥20 IU/kg 3 times/week: Extended ABR, overall	n (missing)	19 (0)		19 (0)
	Mean (SD)	2.78 (7.41)		2.78 (7.41)
	95% CI	-0.79 - 6.35		-0.79 - 6.35
	Median	0.87		0.87
	Min - Max	0.0 - 32.8		0.0 - 32.8
Subgroups by previous treatment				
PUPs: Extended ABR, overall	n (missing)	10 (0)	2 (0)	12 (0)
	Mean (SD)	1.74 (2.58)	0.00 (0.00)	1.45 (2.43)
	95% CI (t-Test)	-0.11 - 3.59	0.00 - 0.00	-0.10 - 2.99
	t-Test			0.0623
	Median	0.60	0.00	0.24
	Min - Max	0.0 - 8.1	0.0 - 0.0	0.0 - 8.1
PTPs: Extended ABR, overall	n (missing)	48 (0)	2 (0)	50 (0)
	Mean (SD)	4.93 (11.40)	0.00 (0.00)	4.74 (11.21)
	95% CI (t-Test)	1.62 - 8.25	0.00 - 0.00	1.55 - 7.92
	t-Test			0.0043
	Median	0.92	0.00	0.88
	Min - Max	0.0 - 60.3	0.0 - 0.0	0.0 - 60.3

Source: Appendix Tables 14.3.2.1.b, 14.3.2.1.1.b, 14.3.2.1.2.b

ABR = annual bleeding rate, CI = confidence interval, FAS = Full Analysis Set, IU = international units, N = number in analysis population, n = number of patients with event / in category, PTP = previously treated patient, PUP = previously untreated patient, SD = standard deviation.

ABR = (number of bleeds at end of year visit*365.25)/patients annual observation time [days]. Annual observation time = time between current and previous end of year visit. Overall observation time = sum of annual observation times. Bleedings before first visit / informed consent and after final end of year visit not included in ABR calculation.

The t-test compares the mean ABR between the severe and non-severe subgroups; however, the results are only shown if there were at least 2 observations per subgroup.

Previously (un)treated as documented at baseline on form “Prior and/or other treatment for hemophilia A (other than Haemoctin)”.

In the total PSAF, the median extended ABR was 14.59 (Table 21). The median extended ABR in the “Prophylaxis <20 IU/kg 3 times/week” subgroup was higher than in the “Prophylaxis ≥20 IU/kg 3 times/week” subgroup (10.81 vs. 4.30). The median extended ABR of PUPs was higher than of PTPs (33.79 vs. 13.05) (Table 21).

In the total SAF, the median extended ABR was 0.68 (Table 22). The median extended ABR in the “Prophylaxis <20 IU/kg 3 times/week” subgroup was higher than in the “Prophylaxis ≥20 IU/kg 3 times/week” subgroup (2.67 vs. 0.29). The median extended ABR of PUPs was smaller than of PTPs (0.00 vs. 0.75) (Table 22).

Table 21 Extended annual bleeding rate based on Bleeding Page in the PSAF and in subgroups by treatment regimen and previous treatment (PSAF)

(Sub)population: Extended ABR, overall	Statistics	Hemophilia status		Total
		Severe (N=47)	Non-severe (N=1)	(N=48)
PSAF: Extended ABR, overall	n (missing)	47 (0)	1 (0)	48 (0)
	Mean (SD)	20.75 (19.14)	0.41 (-)	20.32 (19.17)
	95% CI	15.13 - 26.37	-	14.76 - 25.89
	Median	15.51	0.41	14.59
	Min - Max	0.0 - 98.4	0.4 - 0.4	0.0 - 98.4
Subgroups by treatment regimen				
Prophylaxis: Extended ABR, overall	n (missing)	46 (0)	1 (0)	47 (0)
	Mean (SD)	20.95 (19.30)	0.41 (-)	20.52 (19.33)
	95% CI	15.22 - 26.69	-	14.84 - 26.19
	Median	15.59	0.41	15.51
	Min - Max	0.0 - 98.4	0.4 - 0.4	0.0 - 98.4
Prophylaxis <20 IU/kg 3 times/week: Extended ABR, overall	n (missing)	5 (0)	1 (0)	6 (0)
	Mean (SD)	19.20 (20.16)	0.41 (-)	16.07 (19.60)
	95% CI	-5.84 - 44.24	-	-4.50 - 36.64
	Median	11.28	0.41	10.81
	Min - Max	5.8 - 54.9	0.4 - 0.4	0.4 - 54.9
Prophylaxis ≥20 IU/kg 3 times/week: Extended ABR, overall	n (missing)	12 (0)		12 (0)
	Mean (SD)	12.27 (14.81)		12.27 (14.81)
	95% CI	2.86 - 21.68		2.86 - 21.68
	Median	4.30		4.30
	Min - Max	0.0 - 40.5		0.0 - 40.5
Subgroups by previous treatment				
PUPs: Extended ABR, overall	n (missing)	9 (0)		9 (0)
	Mean (SD)	38.75 (29.32)		38.75 (29.32)
	95% CI (t-Test)	16.21 - 61.29		16.21 - 61.29
	Median	33.79		33.79
	Min - Max	1.2 - 98.4		1.2 - 98.4
PTPs: Extended ABR, overall	n (missing)	38 (0)	1 (0)	39 (0)
	Mean (SD)	16.48 (13.13)	0.41 (-)	16.07 (13.21)
	95% CI (t-Test)	12.17 - 20.80	-	11.79 - 20.35
	Median	13.29	0.41	13.05
	Min - Max	0.0 - 54.9	0.4 - 0.4	0.0 - 54.9

Source: Appendix Tables 14.3.2.2.b, 14.3.2.2.1.b, 14.3.2.2.2.b

ABR = annual bleeding rate, CI = confidence interval, IU = international units, N = number in analysis population, n = number of patients with event / in category, PSAF = Pooled Safety Analysis Set, PTP = previously treated patient, PUP = previously untreated patient, SD = standard deviation.

ABR = (number of bleeds at end of year visit*365.25)/patients annual observation time [days] based on bleedings before first visit / informed consent and after final end of year visit not included in ABR calculation. Annual observation time = time between current and previous end of year visit. Overall observation time = sum of annual observation times.

The t-test compares the mean ABR between the severe and non-severe subgroups; however, the results are only shown if there were at least 2 observations per subgroup.

Previously (un)treated as documented at baseline on form “Prior and/or other treatment for hemophilia A (other than Haemoctin)”.

Table 22 Extended annual bleeding rate based on Bleeding Page in the SAF and in subgroups by treatment regimen and previous treatment (SAF)

(Sub)population: Extended ABR, overall	Statistics	Hemophilia status: Severe (N=72)	Hemophilia status: Non-severe (N=8)	Total (N=80)
SAF: Extended ABR, overall	n (missing)	72 (0)	8 (0)	80 (0)
	Mean (SD)	5.56 (17.23)	0.93 (2.35)	5.09 (16.41)
	95% CI	1.51 - 9.61	-1.03 - 2.89	1.44 - 8.75
	t-Test			0.0383
	Median	0.78	0.00	0.68
	Min - Max	0.0 - 125.5	0.0 - 6.7	0.0 - 125.5
Subgroups by treatment regimen				
Prophylaxis: Extended ABR, overall	n (missing)	71 (0)	4 (0)	75 (0)
	Mean (SD)	5.57 (17.35)	0.00 (0.00)	5.27 (16.92)
	95% CI	1.46 - 9.68	0.00 - 0.00	1.38 - 9.17
	t-Test			0.0086
	Median	0.72	0.00	0.65
	Min - Max	0.0 - 125.5	0.0 - 0.0	0.0 - 125.5
Prophylaxis <20 IU/kg 3 times/week: Extended ABR, overall	n (missing)	12 (0)	2 (0)	14 (0)
	Mean (SD)	9.86 (17.11)	0.00 (0.00)	8.45 (16.14)
	95% CI	-1.01 - 20.73	0.00 - 0.00	-0.86 - 17.77
	t-Test			0.0712
	Median	4.05	0.00	2.67
	Min - Max	0.2 - 60.3	0.0 - 0.0	0.0 - 60.3
Prophylaxis ≥20 IU/kg 3 times/week: Extended ABR, overall	n (missing)	26 (0)		26 (0)
	Mean (SD)	2.06 (6.40)		2.06 (6.40)
	95% CI	-0.52 - 4.65		-0.52 - 4.65
	Median	0.29		0.29
	Min - Max	0.0 - 32.8		0.0 - 32.8
Subgroups by previous treatment				
PUPs: Extended ABR, overall	n (missing)	11 (0)	2 (0)	13 (0)
	Mean (SD)	1.58 (2.51)	0.00 (0.00)	1.34 (2.36)
	95% CI (t-Test)	-0.10 - 3.26	0.00 - 0.00	-0.09 - 2.77
	t-Test			0.0630
	Median	0.48	0.00	0.00
	Min - Max	0.0 - 8.1	0.0 - 0.0	0.0 - 8.1
PTPs: Extended ABR, overall	n (missing)	60 (0)	5 (0)	65 (0)
	Mean (SD)	6.33 (18.78)	1.49 (2.93)	5.96 (18.09)
	95% CI (t-Test)	1.48 - 11.18	-2.15 - 5.13	1.47 - 10.44
	t-Test			0.0862
	Median	0.85	0.00	0.75
	Min - Max	0.0 - 125.5	0.0 - 6.7	0.0 - 125.5

Source: Appendix Tables 14.3.2.3.b, 14.3.2.3.1.b, 14.3.2.3.2.b

ABR = annual bleeding rate, CI = confidence interval, IU = international units, N = number in analysis population, n = number of patients with event / in category, PTP = previously treated patient, PUP = previously untreated patient, SAF = Safety Analysis Set, SD = standard deviation.

ABR = (number of bleeds at end of year visit*365.25)/patients annual observation time [days] based on patients at visit with bleeding documentation. Annual observation time = time between current and previous end of year visit. Overall observation time = sum of annual observation times.

The t-test compares the mean ABR between the severe and non-severe subgroups; however, the results are only shown if there were at least 2 observations per subgroup.

Previously (un)treated as documented at baseline on form “Prior and/or other treatment for hemophilia A (other than Haemoctin)”.

Comparing the 3 analyzed populations, the median extended ABR was similar between the FAS and the SAF (e.g., 0.72 in the total FAS and 0.68 in the total SAF) but clearly higher in the PSAF (e.g., 14.59 in the total PSAF).

Comparing the original median ABR solely based on the Joint-Bleeds eCRF Instrument and the extended median ABR, the latter was usually higher (e.g., in the total FAS 0.12 vs. 0.72; in the total PSAF 13.34 [Source: Appendix Table 14.3.2.2] vs. 14.59). This result was expected because the original ABRs only referred to joint bleedings, whereas the extended ABRs included all types of bleeding, including non-joint bleedings.

For the low median ABRs in the FAS (especially ABRs <1), the relative difference between original and extended median ABRs appears greater than for the higher ABRs in the PSAF:

- **FAS:** total FAS (n=64 patients): 0.12 vs. 0.72; Prophylaxis (n=61 patients): 0.24 vs. 0.72; Prophylaxis <20 IU/kg 3 times/week (n=12 patients): 2.47 vs. 2.67; Prophylaxis ≥20 IU/kg 3 times/week (n=19 patients): 0.00 vs.0.87; PUPs (n=12 patients): 0.24 both; PTPs (n=50 patients): 0.24 vs. 0.88.
- **PSAF:** total PSAF (n=48 patients): 13.34 vs. 14.59; Prophylaxis (n=47 patients): 13.48 vs. 15.51; Prophylaxis <20 IU/kg 3 times/week (n=6 patients): 9.98 vs. 10.81; Prophylaxis ≥20 IU/kg 3 times/week (n=12 patients): 4.01 vs.4.30; PUPs (n=9 patients): 33.94 vs. 33.79; PTPs (n=39 patients): 12.88 vs. 13.05.

12.4.6 Formation of Factor VIII Inhibitors

One of the secondary objectives of this study was the evaluation of the occurrence and the characterization of FVIII inhibitors. However, no FVIII inhibitor formation was observed during this study (Appendix Tables 14.4.1.1.1 and 14.4.1.2.1).

12.4.7 Bleeding Score

The bleeding score assesses the musculoskeletal outcome in hemophilia and takes into account the number and severity of joint bleedings per year. Minor joint bleedings are characterized by mild pain, minimal swelling, minimal restriction of motion and resolve within 24 h of treatment. Major joint bleedings are characterized by pain, effusion, limitation of motion and fail to respond to treatment within 24 h. The bleeding score ranges from 0 to 3, where:

- 0 = no joint bleeding per year
- 1 = no major joint bleeding, 1–3 minor joint bleedings per year
- 2 = 1–2 major, or 4–6 minor joint bleedings per year
- 3 = 3 or more major joint bleedings or 7 or more minor joint bleedings per year

Therefore, a lower bleeding score indicates a better musculoskeletal outcome (Observation Plan, version 2.0, dated 18-Feb-2021, Annex 2).

Bleeding score data in the FAS including subgroups by treatment regimen are shown in Table 23. The associated bleeding score data in each individual year of treatment are shown in Appendix Tables 14.4.1.3.1 and 14.4.1.3.1.1.

In the total FAS, the median bleeding score was 0.33 based on data of the 64 patients with bleeding documentation (Table 23).

Compared with the total FAS, in the "Prophylaxis" subgroup of the FAS, the median bleeding score was the same (0.33). In the "Prophylaxis <20 IU/kg 3 times/week" subgroup of the FAS, the median bleeding score was higher than in the "Prophylaxis ≥20 IU/kg 3 times/week" subgroup of the FAS (1.25 vs. 0.25) (Table 23), implying that the higher dose of prophylactic treatment is associated with a better joint outcome, with low sample sizes in the specific prophylaxis subgroups.

Table 23 Overall bleeding score in the FAS and in subgroups by treatment regimen (FAS)

(Sub)population: Bleeding score, overall	Statistics	Hemophilia status: Severe (N=72)	Hemophilia status: Non-severe (N=8)	Total (N=80)
FAS: Bleeding score, overall	n (missing)	59 (0)	5 (0)	64 (0)
	Mean (SD)	1.01 (1.13)	0.00 (0.00)	0.93 (1.12)
	Median	0.67	0.00	0.33
	Min - Max	0.0 - 3.0	0.0 - 0.0	0.0 - 3.0
Subgroups by treatment regimen				
Prophylaxis: Bleeding score, overall	n (missing)	58 (0)	3 (0)	61 (0)
	Mean (SD)	0.97 (1.11)	0.00 (0.00)	0.93 (1.10)
	Median	0.50	0.00	0.33
	Min - Max	0.0 - 3.0	0.0 - 0.0	0.0 - 3.0
Prophylaxis <20 IU/kg 3 times/week: Bleeding score, overall	n (missing)	11 (0)	1 (0)	12 (0)
	Mean (SD)	1.18 (0.78)	0.00 (.)	1.08 (0.82)
	Median	1.50	0.00	1.25
	Min - Max	0.0 - 2.0	0.0 - 0.0	0.0 - 2.0
Prophylaxis ≥20 IU/kg 3 times/week: Bleeding score, overall	n (missing)	19 (0)		19 (0)
	Mean (SD)	0.61 (0.87)		0.61 (0.87)
	Median	0.25		0.25
	Min - Max	0.0 - 3.0		0.0 - 3.0

Source: Appendix Tables 14.4.1.3.1, 14.4.1.3.1.1

N = number in analysis population, n = number of patients with event / in category, FAS = Full Analysis Set, SD = standard deviation.

12.4.8 Number, Severity and Location of Bleedings

12.4.8.1 Number and Severity of Bleedings

In the SAF, 794 (100%) bleeding events were recorded overall. The majority of bleeding events (601, 75.7%) were mild, followed by 126 (15.9%) moderate bleedings and 4 (0.5%)

severe bleedings (information on the severity of 63 [7.9%] bleedings was missing). A similar distribution is seen in the subgroups, where, however, the proportion of patients with missing data varied (Table 24).

The number and severity of bleedings in the FAS and subgroups by treatment regimen are shown in Appendix Tables 14.4.1.4.1.1 and 14.4.1.4.1.1.1.

Table 24 Number and severity of bleedings by treatment regimen (SAF)

(Sub)population Number/Severity of Bleeding Events	Hemophilia status Severe (N=72) n	 %	Non-severe (N=8) n	 %	Total (N=80) n	 %
SAF						
Total Bleeding Events	784	100	10	100	794	100
Severity						
mild	593	75.6	8	80	601	75.7
moderate	125	15.9	1	10	126	15.9
severe	3	0.4	1	10	4	0.5
missing	63	8.0			63	7.9
Subgroups by treatment regimen						
Prophylaxis	(N=71)		(N=4)		(N=75)	
Total Bleeding Events	768	100	2	100	770	100
Severity						
mild	577	75.1			577	74.9
moderate	125	16.3	1	50.0	126	16.4
severe	3	0.4	1	50.0	4	0.5
missing	63	8.2			63	8.2

Source: Appendix Tables 14.4.1.4.1.3, 14.4.1.4.1.3.1

N = number in analysis population, n = number of patients with event / in category, SAF = Safety Analysis Set.

12.4.8.2 Location of Bleedings

The number and location of bleedings by location including subgroups by treatment regimen is shown in Appendix Tables 14.4.1.4.2.1 and 14.4.1.4.2.1.1 for the FAS, Appendix Tables 14.4.1.4.2.2 and 14.4.1.4.2.2.1 for the PSAF and Appendix Tables 14.4.1.4.2.3 and 14.4.1.4.2.3.1 for the SAF.

In the SAF, 307 bleedings were documented with a specification of the location. The most common locations (≥5% of locations in the total SAF) were the right elbow (60 [18.0%]), the left elbow joint (28 [8.4%]), the left knee joint (26 [7.8%]), the right ankle joint (19 [5.7%]) and the left ankle joint (18 [5.4%]) (location information was missing for 17 [5.1%] locations; Appendix Tables 14.4.1.4.2.3).

When the left and right sides are combined, bleeding occurred by far most frequently in the elbow (total: 76, left: 16, right: 60), followed by the knee joint (total: 39, left: 26, right: 13),

elbow joint (total: 38, left: 28, right: 10), knee (total: 38, left: 23, right: 15) and ankle joint (total: 37, left: 18, right: 19). The other locations occurred 13 times or less. The distribution between left and right was not equal and varied between the different joints.

In the PSAF, 16535 bleedings were documented with a location. The most common locations (≥3% patients in the total PSAF) were an elbow (732 [4.4%]), a knee (681 [4.1%]) and an ankle (626 [3.8%]) (Tables 14.4.1.4.2.2).

While in the current NIS the locations were prespecified in the eCRF, in the previous NIS, bleeding events included patient-reported single bleeds, which were not coded (meaning that e.g., “left elbow”, “l. elbow”, “l.elbow”, “elbow left” and “elbow l.” are considered separate categories). The inconsistent specification of location between the two studies prevents a direct comparison.

12.4.9 Quality of Life

One of the secondary objectives of this study was the evaluation of QoL determined with the Euroqol EQ-5D in adults and the EQ-5D-Y in adolescents. The questionnaires cover the domains “Mobility”, “Self-Care”, “Doing usual activities”, “Pain/Discomfort”, “Anxiety/Depression” and “Visual Analogue Scale (VAS)”.

At baseline in the total SAF (N=80), between 60 (“VAS”) and 71 (“Anxiety/Depression”) patients for the various domains returned a completed questionnaire. Response rates decreased during the course of the study: Between 56 and 59 patients completed the questionnaire at end of Year 1 documentation, between 30 and 31 patients at end of Year 2 documentation and between 22 and 25 patients at end of Year 3 documentation (Table 25 shows results for baseline and end of Year 1 to Year 3 documentation; results for all visits are shown in Appendix Table 14.4.2.2).

In the domains “Mobility”, “Self-Care”, “Doing usual activities”, “Pain/Discomfort” and “Anxiety/Depression” the median change from baseline at end of Year 1, 2 and 3 documentation was zero. So, for these domains, no noticeable changes were observed in the SAF (Table 25).

The VAS ranges from 0 (zero; worst imaginable health) to 100 (best imaginable health). In the SAF, the median VAS was 70 at baseline, 75 at end of Year 1 documentation, 72.5 at end of Year 2 documentation and 67.5 at end of Year 3 documentation, suggesting a slight improvement in patient-reported health in Year 1 and 2. Correspondingly, the median change from baseline for the VAS was 1.5 at end of Year 1 and 2 documentation and zero at end of Year 3 documentation, supporting a mild improvement in patient-reported health in Year 1 and 2 (Table 25).

Quality of life results for the FAS are shown in Appendix Table 14.4.2.1. Like in the SAF, in the FAS no changes were observed for the domains “Mobility”, “Self-Care”, “Doing usual activities”, “Pain/Discomfort” and “Anxiety/Depression”. Like in the SAF, in the FAS a mild improvement in patient-reported health was observed in year 1 and 2.

Table 25 Quality of Life (SAF)

Parameter	Visit	Statistics	Hemophilia status: Severe (N=72) Value	Severe (N=72) Change from BL	Non-severe (N=8) Value	Non-severe (N=8) Change from BL	Total (N=80) Value	Total (N=80) Change from BL
Mobility	Baseline	n (missing)	66 (6)	-	4 (4)	-	70 (10)	-
		Mean (SD)	1.64 (0.52)	-	1.00 (0.00)	-	1.60 (0.52)	-
		Median	2.00	-	1.00	-	2.00	-
		Min - Max	1.0 - 3.0	-	1.0 - 1.0	-	1.0 - 3.0	-
	Year 1*	n (missing)	55 (17)	53 (19)	4 (4)	3 (5)	59 (21)	56 (24)
		Mean (SD)	1.64 (0.52)	-0.13 (1.06)	1.25 (0.50)	0.33 (0.58)	1.61 (0.53)	-0.11 (1.04)
		Median	2.00	0.00	1.00	0.00	2.00	0.00
		Min - Max	1.0 - 3.0	-7.0 - 1.0	1.0 - 2.0	0.0 - 1.0	1.0 - 3.0	-7.0 - 1.0
	Year 2*	n (missing)	28 (44)	26 (46)	3 (5)	2 (6)	31 (49)	28 (52)
		Mean (SD)	1.64 (0.56)	0.12 (0.43)	1.00 (0.00)	0.00 (0.00)	1.58 (0.56)	0.11 (0.42)
		Median	2.00	0.00	1.00	0.00	2.00	0.00
		Min - Max	1.0 - 3.0	-1.0 - 1.0	1.0 - 1.0	0.0 - 0.0	1.0 - 3.0	-1.0 - 1.0
	Year 3*	n (missing)	23 (49)	21 (51)	1 (7)	1 (7)	24 (56)	22 (58)
		Mean (SD)	1.43 (0.51)	-0.05 (0.38)	1.00 (.)	0.00 (.)	1.42 (0.50)	-0.05 (0.38)
		Median	1.00	0.00	1.00	0.00	1.00	0.00
		Min - Max	1.0 - 2.0	-1.0 - 1.0	1.0 - 1.0	0.0 - 0.0	1.0 - 2.0	-1.0 - 1.0
Self-Care	Baseline	n (missing)	63 (9)	-	4 (4)	-	67 (13)	-
		Mean (SD)	1.27 (0.48)	-	1.00 (0.00)	-	1.25 (0.47)	-
		Median	1.00	-	1.00	-	1.00	-
		Min - Max	1.0 - 3.0	-	1.0 - 1.0	-	1.0 - 3.0	-
	Year 1*	n (missing)	55 (17)	52 (20)	4 (4)	3 (5)	59 (21)	55 (25)
		Mean (SD)	1.31 (0.54)	-0.19 (1.56)	1.00 (0.00)	0.00 (0.00)	1.29 (0.53)	-0.18 (1.52)
		Median	1.00	0.00	1.00	0.00	1.00	0.00
		Min - Max	1.0 - 3.0	-8.0 - 2.0	1.0 - 1.0	0.0 - 0.0	1.0 - 3.0	-8.0 - 2.0
	Year 2*	n (missing)	28 (44)	25 (47)	3 (5)	2 (6)	31 (49)	27 (53)
		Mean (SD)	1.32 (0.61)	-0.12 (1.81)	1.00 (0.00)	0.00 (0.00)	1.29 (0.59)	-0.11 (1.74)
		Median	1.00	0.00	1.00	0.00	1.00	0.00
		Min - Max	1.0 - 3.0	-8.0 - 2.0	1.0 - 1.0	0.0 - 0.0	1.0 - 3.0	-8.0 - 2.0
	Year 3*	n (missing)	24 (48)	21 (51)	1 (7)	1 (7)	25 (55)	22 (58)
		Mean (SD)	1.25 (0.53)	-0.29 (1.87)	1.00 (.)	0.00 (.)	1.24 (0.52)	-0.27 (1.83)
		Median	1.00	0.00	1.00	0.00	1.00	0.00
		Min - Max	1.0 - 3.0	-8.0 - 2.0	1.0 - 1.0	0.0 - 0.0	1.0 - 3.0	-8.0 - 2.0

Parameter	Visit	Statistics	Hemophilia status: Severe (N=72) Value	Severe (N=72) Change from BL	Non-severe (N=8) Value	Non-severe (N=8) Change from BL	Total (N=80) Value	Total (N=80) Change from BL
Doing usual activities	Baseline	n (missing)	65 (7)	-	4 (4)	-	69 (11)	-
		Mean (SD)	1.40 (0.55)	-	1.00 (0.00)	-	1.38 (0.55)	-
		Median	1.00	-	1.00	-	1.00	-
		Min - Max	1.0 - 3.0	-	1.0 - 1.0	-	1.0 - 3.0	-
	Year 1*	n (missing)	55 (17)	52 (20)	4 (4)	3 (5)	59 (21)	55 (25)
		Mean (SD)	1.51 (0.54)	-0.02 (1.13)	1.00 (0.00)	0.00 (0.00)	1.47 (0.54)	-0.02 (1.10)
		Median	1.00	0.00	1.00	0.00	1.00	0.00
		Min - Max	1.0 - 3.0	-7.0 - 1.0	1.0 - 1.0	0.0 - 0.0	1.0 - 3.0	-7.0 - 1.0
	Year 2*	n (missing)	28 (44)	25 (47)	3 (5)	2 (6)	31 (49)	27 (53)
		Mean (SD)	1.50 (0.64)	0.20 (0.50)	1.00 (0.00)	0.00 (0.00)	1.45 (0.62)	0.19 (0.48)
		Median	1.00	0.00	1.00	0.00	1.00	0.00
		Min - Max	1.0 - 3.0	-1.0 - 1.0	1.0 - 1.0	0.0 - 0.0	1.0 - 3.0	-1.0 - 1.0
	Year 3*	n (missing)	24 (48)	21 (51)	1 (7)	1 (7)	25 (55)	22 (58)
		Mean (SD)	1.46 (0.59)	0.19 (0.40)	1.00 (.)	0.00 (.)	1.44 (0.58)	0.18 (0.39)
		Median	1.00	0.00	1.00	0.00	1.00	0.00
		Min - Max	1.0 - 3.0	0.0 - 1.0	1.0 - 1.0	0.0 - 0.0	1.0 - 3.0	0.0 - 1.0
Pain/Discomfort	Baseline	n (missing)	64 (8)	-	4 (4)	-	68 (12)	-
		Mean (SD)	1.69 (0.59)	-	1.25 (0.50)	-	1.66 (0.59)	-
		Median	2.00	-	1.00	-	2.00	-
		Min - Max	1.0 - 3.0	-	1.0 - 2.0	-	1.0 - 3.0	-
	Year 1*	n (missing)	54 (18)	51 (21)	4 (4)	3 (5)	58 (22)	54 (26)
		Mean (SD)	1.63 (0.52)	-0.02 (1.38)	1.50 (0.58)	0.33 (0.58)	1.62 (0.52)	0.00 (1.35)
		Median	2.00	0.00	1.50	0.00	2.00	0.00
		Min - Max	1.0 - 3.0	-6.0 - 7.0	1.0 - 2.0	0.0 - 1.0	1.0 - 3.0	-6.0 - 7.0
	Year 2*	n (missing)	28 (44)	24 (48)	3 (5)	2 (6)	31 (49)	26 (54)
		Mean (SD)	1.75 (0.52)	0.00 (0.51)	1.33 (0.58)	0.00 (0.00)	1.71 (0.53)	0.00 (0.49)
		Median	2.00	0.00	1.00	0.00	2.00	0.00
		Min - Max	1.0 - 3.0	-1.0 - 1.0	1.0 - 2.0	0.0 - 0.0	1.0 - 3.0	-1.0 - 1.0
	Year 3*	n (missing)	24 (48)	20 (52)	1 (7)	1 (7)	25 (55)	21 (59)
		Mean (SD)	1.46 (0.51)	-0.20 (0.41)	2.00 (.)	1.00 (.)	1.48 (0.51)	-0.14 (0.48)
		Median	1.00	0.00	2.00	1.00	1.00	0.00
		Min - Max	1.0 - 2.0	-1.0 - 0.0	2.0 - 2.0	1.0 - 1.0	1.0 - 2.0	-1.0 - 1.0

Parameter	Visit	Statistics	Hemophilia status: Severe (N=72) Value	Severe (N=72) Change from BL	Non-severe (N=8) Value	Non-severe (N=8) Change from BL	Total (N=80) Value	Total (N=80) Change from BL
Anxiety/Depression	Baseline	n (missing)	67 (5)	-	4 (4)	-	71 (9)	-
		Mean (SD)	1.36 (0.57)	-	1.25 (0.50)	-	1.35 (0.56)	-
		Median	1.00	-	1.00	-	1.00	-
		Min - Max	1.0 - 3.0	-	1.0 - 2.0	-	1.0 - 3.0	-
	Year 1*	n (missing)	54 (18)	53 (19)	4 (4)	3 (5)	58 (22)	56 (24)
		Mean (SD)	1.19 (0.39)	-0.04 (1.11)	1.00 (0.00)	-0.33 (0.58)	1.17 (0.38)	-0.05 (1.09)
		Median	1.00	0.00	1.00	0.00	1.00	0.00
		Min - Max	1.0 - 2.0	-2.0 - 7.0	1.0 - 1.0	-1.0 - 0.0	1.0 - 2.0	-2.0 - 7.0
	Year 2*	n (missing)	28 (44)	26 (46)	3 (5)	2 (6)	31 (49)	28 (52)
		Mean (SD)	1.07 (0.26)	-0.15 (0.37)	1.00 (0.00)	-0.50 (0.71)	1.06 (0.25)	-0.18 (0.39)
		Median	1.00	0.00	1.00	-0.50	1.00	0.00
		Min - Max	1.0 - 2.0	-1.0 - 0.0	1.0 - 1.0	-1.0 - 0.0	1.0 - 2.0	-1.0 - 0.0
	Year 3*	n (missing)	24 (48)	22 (50)	1 (7)	1 (7)	25 (55)	23 (57)
		Mean (SD)	1.21 (0.41)	0.00 (0.44)	1.00 (.)	-1.00 (.)	1.20 (0.41)	-0.04 (0.47)
		Median	1.00	0.00	1.00	-1.00	1.00	0.00
		Min - Max	1.0 - 2.0	-1.0 - 1.0	1.0 - 1.0	-1.0 - -1.0	1.0 - 2.0	-1.0 - 1.0
VAS	Baseline	n (missing)	56 (16)	-	4 (4)	-	60 (20)	-
		Mean (SD)	60.86 (30.43)	-	63.50 (36.41)	-	61.03 (30.51)	-
		Median	70.00	-	80.00	-	70.00	-
		Min - Max	5.0 - 100.0	-	9.0 - 85.0	-	5.0 - 100.0	-
	Year 1*	n (missing)	52 (20)	43 (29)	4 (4)	3 (5)	56 (24)	46 (34)
		Mean (SD)	73.00 (19.07)	13.86 (32.15)	59.38 (42.71)	-10.17 (26.36)	72.03 (21.20)	12.29 (32.12)
		Median	75.00	2.00	65.00	-0.50	75.00	1.50
		Min - Max	6.0 - 100.0	-40.0 - 92.0	8.5 - 99.0	-40.0 - 10.0	6.0 - 100.0	-40.0 - 92.0
	Year 2*	n (missing)	27 (45)	20 (52)	3 (5)	2 (6)	30 (50)	22 (58)
		Mean (SD)	68.04 (20.09)	6.00 (28.00)	83.33 (5.77)	5.00 (7.07)	69.57 (19.64)	5.91 (26.68)
		Median	65.00	1.50	80.00	5.00	72.50	1.50
		Min - Max	20.0 - 98.0	-35.0 - 60.0	80.0 - 90.0	0.0 - 10.0	20.0 - 98.0	-35.0 - 60.0
	Year 3*	n (missing)	21 (51)	13 (59)	1 (7)	1 (7)	22 (58)	14 (66)
		Mean (SD)	68.48 (20.12)	1.08 (27.77)	90.00 (.)	10.00 (.)	69.45 (20.16)	1.71 (26.79)
		Median	65.00	0.00	90.00	10.00	67.50	0.00
		Min - Max	30.0 - 98.0	-40.0 - 55.0	90.0 - 90.0	10.0 - 10.0	30.0 - 98.0	-40.0 - 55.0

Source: Appendix Table 14.4.2.2. BL = baseline, N = number in analysis population, n = number of patients with event / in category, SAF = Safety Analysis Set, SD = standard deviation, VAS = Visual Analogue Scale. * End of year documentation. For adolescents the EQ-5D-Y was used until the patient became adult with 18 years and the EQ-5-D was used from then on.

12.5 Other Analyses

This section displays the results of further relevant variables.

12.5.1 Clinical Laboratory Parameters

A summary of the clinical laboratory parameters hemoglobin, platelets, inhibitors and blood glucose are shown for baseline and the end of Year 1 to Year 3 documentation in the total SAF in Table 26. Overall, no meaningful changes in laboratory parameters were found. In detail:

The median baseline hemoglobin value was 9.31 mmol/l. The median change from this value in Years 1, 2 and 3 was 0.00 mmol/l each (Table 26).

The median baseline platelets value was 246.0 $x10^9$/L. The median change from this value in Year 1, Year 2 and Year 3 was -8.0 $x10^9$/L, 0.5 $x10^9$/L and 0.0 $x10^9$/L (Table 26).

The median baseline blood glucose value was 5.00 mmol/L. The median change from this value in Year 1, Year 2 and Year 3 was 0.00 mmol/L, 0.15 mmol/L and 0.40 mmol/L. The changes in Year 2 and Year 3 may in part be explained by the low number of patients included in the analysis, i.e., 8 and 5 patients, respectively (Table 26).

Collectively, no marked changes were observed in the laboratory values evaluated.

Table 26 Clinical laboratory parameters: summary statistics (SAF)

Parameter	Visit	Statistics	Total (N=80) Value	Total (N=80) Change from BL
Hemoglobin [mmol/l]	Baseline	n (missing)	67 (13)	-
		Mean (SD)	10.61 (10.80)	-
		Median	9.31	-
		Min - Max	6.5 - 96.2	-
	Year 1*	n (missing)	58 (22)	49 (31)
		Mean (SD)	9.25 (0.96)	-1.70 (12.46)
		Median	9.34	0.00
		Min - Max	6.0 - 10.7	-86.9 - 2.5
	Year 2*	n (missing)	29 (51)	22 (58)
		Mean (SD)	8.86 (0.87)	-0.00 (0.62)
		Median	9.00	0.00
		Min - Max	6.6 - 10.4	-1.1 - 1.4
	Year 3*	n (missing)	20 (60)	15 (65)
		Mean (SD)	8.76 (0.73)	-0.10 (0.55)
		Median	8.81	0.00
		Min - Max	7.0 - 9.9	-1.0 - 0.6
Platelets [x10^9/L]	Baseline	n (missing)	67 (13)	-
		Mean (SD)	253.6 (85.5)	-
		Median	246.0	-
		Min - Max	83 - 580	-
	Year 1*	n (missing)	58 (22)	49 (31)
		Mean (SD)	245.6 (70.8)	-22.4 (75.8)
		Median	242.0	-8.0
		Min - Max	108 - 424	-405 - 61
	Year 2*	n (missing)	27 (53)	22 (58)
		Mean (SD)	270.0 (50.3)	1.5 (29.8)
		Median	262.0	0.5
		Min - Max	195 - 349	-75 - 44
	Year 3*	n (missing)	20 (60)	15 (65)
		Mean (SD)	273.7 (76.8)	9.5 (67.4)
		Median	269.0	0.0
		Min - Max	148 - 501	-121 - 211
Blood Glucose [mmol/L]	Baseline	n (missing)	38 (42)	-
		Mean (SD)	5.55 (2.71)	-
		Median	5.00	-
		Min - Max	2.7 - 19.9	-
	Year 1*	n (missing)	34 (46)	28 (44)
		Mean (SD)	5.89 (3.61)	0.48 (1.69)
		Median	5.00	0.00
		Min - Max	3.9 - 24.8	-4.0 - 5.2
	Year 2*	n (missing)	10 (70)	8 (64)
		Mean (SD)	5. 44 (0.78)	0.07 (0.94)
		Median	5.33	0.15
		Min - Max	4.4 - 6.6	-1.3 - 1.6
	Year 3*	n (missing)	6 (74)	5 (75)
		Mean (SD)	5.65 (0.39)	0.30 (1.02)
		Median	5.74	0.40
		Min - Max	4.9 - 6.0	-1.1 - 1.7

Source: Appendix Table 14.5.2.1

BL = Baseline, BU = Bethesda units, N = number in analysis population, n = number of patients with event / in category, SAF = Safety Analysis Set, SD = standard deviation.

* End of year documentation.

12.5.2 Concomitant Treatments

Concomitant treatments in the SAF are shown in Appendix Table 14.6.1.1 and concomitant treatments by treatment regimen in Appendix Table 14.6.1.1.1.

The 3 most frequently used treatments in the SAF by ATC level 2 / preferred term were Analgesics/metamizole in 9 (11.3%) patients, Antihemorrhagics/tranexamic acid in 9 (11.3%) patients as well as Antiinflammatory and antirheumatic products/etoricoxib in 8 (10.0%) patients (Table 27). A total of 21 (26.3%) patients received pain or anti-inflammatory therapy (Analgesics: metamizole, paracetamol; Antiinflammatory and antirheumatic products: etoricoxib, ibuprofen; Topical products for joint and muscular pain: diclofenac), which was therefore the predominant concomitant therapy during the study.

Table 27 Concomitant treatments in ≥2% of all patients (SAF)

ATC LEVEL 2 preferred term*	Hemophilia status Severe (N=72) n	 %	Non-severe (N=8) n	 %	Total (N=80) n	 %
ANALGESICS metamizole**	8	11.1	1	12.5	9	11.3
ANTIHEMORRHAGICS tranexamic acid	6	8.3	3	37.5	9	11.3
ANTIINFLAMMATORY AND ANTIRHEUMATIC PRODUCTS etoricoxib	5	6.9	3	37.5	8	10.0
ANALGESICS paracetamol	5	6.9	1	12.5	6	7.5
AGENTS ACTING ON THE RENIN-ANGIOTENSIN SYSTEM ramipril	5	6.9	0	0.0	5	6.3
DRUGS FOR ACID RELATED DISORDERS pantoprazole	5	6.9	0	0.0	5	6.3
ANTIINFLAMMATORY AND ANTIRHEUMATIC PRODUCTS ibuprofen	4	5.6	0	0.0	4	5.0
ANTIGOUT PREPARATIONS allopurinol	3	4.2	0	0.0	3	3.8
BETA BLOCKING AGENTS bisoprolol	3	4.2	0	0.0	3	3.8
AGENTS ACTING ON THE RENIN-ANGIOTENSIN SYSTEM hydrochlorothiazide;ramipril	2	2.8	0	0.0	2	2.5
AGENTS ACTING ON THE RENIN-ANGIOTENSIN SYSTEM indapamide;perindopril erbumine	2	2.8	0	0.0	2	2.5
ANTIBACTERIALS FOR SYSTEMIC USE amoxicillin	1	1.4	1	12.5	2	2.5
ANTIHEMORRHAGICS efmoroctocog alfa	0	0.0	2	25.0	2	2.5
ANTITHROMBOTIC AGENTS enoxaparin sodium	2	2.8	0	0.0	2	2.5
CALCIUM CHANNEL BLOCKERS amlodipine besilate	2	2.8	0	0.0	2	2.5
COUGH AND COLD PREPARATIONS codeine phosphate;guaifenesin	2	2.8	0	0.0	2	2.5
DRUGS FOR ACID RELATED DISORDERS pantoprazole sodium sesquihydrate	2	2.8	0	0.0	2	2.5
THYROID THERAPY levothyroxine	1	1.4	1	12.5	2	2.5
TOPICAL PRODUCTS FOR JOINT AND MUSCULAR PAIN diclofenac	2	2.8	0	0.0	2	2.5
VACCINES tick-borne encephalitis vaccine inact (k23)	2	2.8	0	0.0	2	2.5

Source: Appendix Table 14.6.1.1

N = number in analysis population, SAF = Safety Analysis Set.

* Coded according to the WHO DD 2022Sep01.

** Coded separately in the source table as "Metamizole" or "Metamizole sodium"; merged manually in this in-text table.

12.5.3 Medical History of Special Interest and Previous and Concomitant Medical Diagnoses

Medical history referred to the last 6 months prior to enrolment. In the SAF, the median total number of surgeries was 0.00 (range 0 to 9) (Table 28). For more information on surgeries, see Table 29.

In the SAF, 9 (11.7%) patients had acute infections, 8 (10.8%) patients had vaccinations, 2 (2.5%) patients had a history of auto-immune disease and 1 (1.3%) patient had a history of malignancy (Table 28).

The results for subgroups by treatment regimen are shown in Appendix Table 14.6.2.1.1.

Table 28 Medical history of special interest/previous and concomitant medical diagnoses (SAF)

Parameter	Statistics	Hemophilia status		Total (N=80)
		Severe (N=72)	Non-severe (N=8)	
Total number of surgeries	n (missing)	72 (0)	8 (0)	80 (0)
	Mean (SD)	0.36 (1.19)	0.00 (0.00)	0.33 (1.13)
	Median	0.00	0.00	0.00
	Min - Max	0 - 9	0 - 0	0 - 9
Patients with any surgical procedure (Medical History)		13 (18.1%)	0 (0.0%)	13 (16.3%)
Patients with vaccinations		8 (11.8%)	0 (0.0%)	8 (10.8%)
Patients with acute infections		9 (12.9%)	0 (0.0%)	9 (11.7%)
Patients with history of malignancy		1 (1.4%)	0 (0.0%)	1 (1.3%)
Patients with history of auto-immune disease		2 (2.8%)	0 (0.0%)	2 (2.5%)
Patients with central device		0 (0.0%)	0 (0.0%)	0 (0.0%)
Patients with history of ICH		0 (0.0%)	0 (0.0%)	0 (0.0%)

Source: Appendix Table 14.6.2.1, Appendix Listing 16.2.5 (for patients with any surgical procedure)

ICH = intracranial hemorrhage, N = number in analysis population, n = number of patients with event / in category, SAF = Safety Analysis Set, SD = standard deviation.

Medical history within the last 6 months prior to enrolment.

In the SAF, 13 (16.3%) patients had at least one surgical procedure within the last 6 months prior to enrolment (Table 29).

The 3 most common surgical procedures were “orthopedic surgery” in 7 (8.8%) patients, “abdominal surgery” in 4 (5.0%) patients and “dental procedure” in 2 (2.5%) patients (Table 29).

Table 29 Medical history: Surgical procedures (SAF)

Surgical Procedure	Hemophilia status					
	Severe (N=72)		Non-severe (N=8)		Total (N=80)	
	n	%	n	%	n	%
Patients with at least one surgical procedure	13	18.1	0	0.0	13	16.3
Orthopedic surgery	7	9.7	0	0.0	7	8.8
Abdominal surgery	4	5.6	0	0.0	4	5.0
Other*	4	5.6	0	0.0	4	5.0
Dental procedure	2	2.8	0	0.0	2	2.5
Neurosurgery	1	1.4	0	0.0	1	1.3

Source: Appendix Table 14.6.2.2

N = number in analysis population, n = number of patients with event / in category, SAF = Safety Analysis Set.

* Free text entries for “Other” were “Hämatomausräumung”, “Portexplantation”, “Pterygium nasal li” and “Herniotomy”, each of which was documented for 1 (1.3%) patient of the total SAF and 1 (1.4%) of the “Severe” subgroup.

Surgeries within the last 6 months prior to enrolment.

12.5.4 Joint Status and Location

In the SAF, 49 (61.3%) patients had affected joints at baseline. Affected joints resulted in an impact on daily life in 41 (51.3%) patients, in walking impairment in 27 (33.8%) patients, in any joint replacements implanted in 9 (11.3%) patients and in miscellaneous effects in 8 (10%) patients (Table 30). The corresponding numbers are decreasing over the end of Year 1 to Year 5 documentations. The decrease is probably largely due to the decreasing number of patients, which has also been seen in the evaluation of QoL (Section 12.4.9) and laboratory parameters (Section 12.5.1).

Joint status in subgroups by treatment regimen is shown in Appendix Table 14.6.3.1.1.

Table 30 Joint status (SAF)

Visit	Parameter	Hemophilia status		
		Severe (N=72)	Non-severe (N=8)	Total (N=80)
Baseline	**Patients with affected joints**	45 (62.5%)	4 (50.0%)	49 (61.3%)
	Impact on daily life	40 (55.6%)	1 (12.5%)	41 (51.3%)
	Walking impairment	27 (37.5%)		27 (33.8%)
	Any joint replacements implanted	9 (12.5%)		9 (11.3%)
	Miscellaneous	6 (8.3%)	2 (25.0%)	8 (10.0%)
Year 1*	**Patients with affected joints**	10 (13.9%)		10 (12.5%)
	Impact on daily life	8 (11.1%)		8 (10.0%)
	Walking impairment	4 (5.6%)		4 (5.0%)
Year 2*	**Patients with affected joints**	6 (8.3%)		6 (7.5%)
	Impact on daily life	6 (8.3%)		6 (7.5%)
Year 3*	**Patients with affected joints**	3 (4.2%)		3 (3.8%)
	Impact on daily life	2 (2.8%)		2 (2.5%)
	Walking impairment	2 (2.8%)		2 (2.5%)
	Any joint replacements implanted	2 (2.8%)		2 (2.5%)
Year 4*	**Patients with affected joints**	7 (9.7%)		7 (8.8%)
	Impact on daily life	6 (8.3%)		6 (7.5%)
	Walking impairment	1 (1.4%)		1 (1.3%)
Year 5*	**Patients with affected joints**	2 (2.8%)		2 (2.5%)
	Impact on daily life	1 (1.4%)		1 (1.3%)
	Walking impairment	2 (2.8%)		2 (2.5%)

Source: Appendix Table 14.6.3.1

N = number in analysis population, n = number of patients with event / in category, SAF = Safety Analysis Set.

* End of year documentation.

Multiple answers regarding impact of affected joints were possible.

Joint location in the SAF and in subgroups by treatment regimen at baseline and end of Year 1 to Year 5 documentation is shown in Appendix Table 14.6.3.2 and 14.6.3.2.1.

12.5.5 Sick Leave

Data on sick leave in the SAF are shown in Table 31 for baseline and end of Year 1 to Year 3 documentation. All results for the SAF and subgroups by treatment regimen are shown in Appendix Tables 14.6.4.1 and 14.6.4.1.1.

The median number of patients overall, students and employees on sick leave was always 0.0 (zero). The maximum number of patients on sick leave ranged from 0 to 5, supporting an overall low number of patients on sick leave. However, these results are based on low patient numbers, i.e., 23 patients overall at baseline and end of Year 1 documentation, 13 at Year 2 documentation and 14 at Year 3 documentation in the total SAF (Table 31).

Table 31 Sick Leave (SAF)

Visit	Activity	Statistics	Hemophilia status: Severe (N=72)	Hemophilia status: Non-severe (N=8)	Total (N=80)
Baseline	Overall	n (missing)	21 (46)	2 (4)	23 (50)
		Mean (SD)	0.5 (1.5)	0.0 (0.0)	0.5 (1.4)
		Median	0.0	0.0	0.0
		Min - Max	0 - 5	0 - 0	0 - 5
	Student	n (missing)	8 (3)	1 (1)	9 (4)
		Mean (SD)	1.3 (2.3)	0.0 (.)	1.1 (2.2)
		Median	0.0	0.0	0.0
		Min - Max	0 - 5	0 - 0	0 - 5
	Employee	n (missing)	13 (13)	1 (2)	14 (15)
		Mean (SD)	0.1 (0.3)	0.0 (.)	0.1 (0.3)
		Median	0.0	0.0	0.0
		Min - Max	0 - 1	0 - 0	0 - 1
Year 1*	Overall	n (missing)	22 (32)	1 (3)	23 (35)
		Mean (SD)	0.2 (1.1)	0.0 (.)	0.2 (1.0)
		Median	0.0	0.0	0.0
		Min - Max	0 - 5	0 - 0	0 - 5
	Student	n (missing)	6 (2)	0 (2)	6 (4)
		Mean (SD)	0.8 (2.0)		0.8 (2.0)
		Median	0.0		0.0
		Min - Max	0 - 5		0 - 5
	Employee	n (missing)	16 (8)	1 (1)	17 (9)
		Mean (SD)	0.0 (0.0)	0.0 (.)	0.0 (0.0)
		Median	0.0	0.0	0.0
		Min - Max	0 - 0	0 - 0	0 - 0
Year 2*	Overall	n (missing)	12 (14)	1 (1)	13 (15)
		Mean (SD)	0.1 (0.3)	0.0 (.)	0.1 (0.3)
		Median	0.0	0.0	0.0
		Min - Max	0 - 1	0 - 0	0 - 1
	Student	n (missing)	6 (5)	0 (1)	6 (6)
		Mean (SD)	0.0 (0.0)		0.0 (0.0)
		Median	0.0		0.0
		Min - Max	0 - 0		0 - 0
	Employee	n (missing)	6 (2)	1 (0)	7 (2)
		Mean (SD)	0.2 (0.4)	0.0 (.)	0.1 (0.4)
		Median	0.0	0.0	0.0
		Min - Max	0 - 1	0 - 0	0 - 1
Year 3*	Overall	n (missing)	13 (15)	1 (1)	14 (16)
		Mean (SD)	0.3 (1.1)	0.0 (.)	0.3 (1.1)
		Median	0.0	0.0	0.0
		Min - Max	0 - 4	0 - 0	0 - 4
	Student	n (missing)	6 (3)		6 (3)
		Mean (SD)	0.0 (0.0)		0.0 (0.0)
		Median	0.0		0.0
		Min - Max	0 - 0		0 - 0
	Employee	n (missing)	7 (7)	1 (1)	8 (8)
		Mean (SD)	0.6 (1.5)	0.0 (.)	0.5 (1.4)
		Median	0.0	0.0	0.0
		Min - Max	0 - 4	0 - 0	0 - 4

Source: Appendix Table 14.6.4.1

N = number in analysis population, n = number of patients with event / in category, SAF = Safety Analysis Set, SD = standard deviation. * End of year documentation.

No information was available on sick days for children and retirees; therefore, the two categories are not shown.

12.5.6 Assessment of Treatment Effectiveness, Tolerance, Handling of Haemoctin SDH and Patient Health

12.5.6.1 Investigators' Assessment of Treatment Effectiveness, Tolerance and Handling of Haemoctin SDH

The investigators' assessment of treatment effectiveness, tolerance and handling of Haemoctin SDH for the SAF was predominantly "very good" or "good" at every end of year documentation. Less good effectiveness ratings were "fair" in only 0-2 patients per year. Less good tolerance ratings were "fair" in 1 patient in Year 1. Less good handling ratings were "satisfactory" in 1-2 patients per year and "fair" in 0-1 patient per year (Table 32).

Results for SAF subgroups by treatment regimen are shown in Appendix Table 14.6.5.3.1. Results for the PSAF and corresponding subgroups by treatment regimen are shown in Appendix Table 14.6.5.2 and Table 14.6.5.2.1. Results for the FAS and corresponding subgroups by treatment regimen are shown in Appendix Table 14.6.5.1 and Table 14.6.5.1.1.

Table 32 Assessment of treatment effectiveness, tolerance and handling of Haemoctin SDH by the investigator (SAF)

Evaluation of	Visit Evaluation by the investigator	Hemophilia status Severe (N=72) n	 %	 Non-severe (N=8) n	 %	 Total (N=80) n	 %
Effectiveness	**Year 1***	**60**		**5**		**65**	
	very good	33	55.0	2	40.0	35	53.8
	good	26	43.3	3	60.0	29	44.6
	fair	1	1.7			1	1.5
	Year 2*	**31**		**4**		**35**	
	very good	14	45.2	1	25.0	15	42.9
	good	17	54.8	3	75.0	20	57.1
	Year 3*	**29**		**2**		**31**	
	very good	8	27.6	1	50.0	9	29.0
	good	19	65.5	1	50.0	20	64.5
	fair	2	6.9			2	6.5
	Year 4*	**15**		**1**		**16**	
	very good	4	26.7			4	25.0
	good	10	66.7	1	100.0	11	68.8
	fair	1	6.7			1	6.3
	Year 5*	**7**		**1**		**8**	
	good	7	100.0	1	100.0	8	100.0

Evaluation of	Visit Evaluation by the investigator	Hemophilia status					
		Severe (N=72)		Non-severe (N=8)		Total (N=80)	
		n	%	n	%	n	%
Tolerance	**Year 1***	**60**		**5**		**65**	
	very good	31	51.7	2	40.0	33	50.8
	good	28	46.7	3	60.0	31	47.7
	fair	1	1.7			1	1.5
	Year 2*	**31**		**4**		**35**	
	very good	13	41.9	1	25.0	14	40.0
	good	18	58.1	3	75.0	21	60.0
	Year 3*	**29**		**2**		**31**	
	very good	10	34.5	1	50.0	11	35.5
	good	19	65.5	1	50.0	20	64.5
	Year 4*	**15**		**1**		**16**	
	very good	4	26.7			4	25.0
	good	11	73.3	1	100.0	12	75.0
	Year 5*	**7**		**1**		**8**	
	good	7	100.0	1	100.0	8	100.0
Handling	**Year 1***	**60**		**5**		**65**	
	very good	28	46.7	2	40.0	30	46.2
	good	30	50.0	3	60.0	33	50.8
	satisfactory	1	1.7			1	1.5
	fair	1	1.7			1	1.5
	Year 2*	**31**		**4**		**35**	
	very good	8	25.8	2	50.0	10	28.6
	good	22	71.0	2	50.0	24	68.6
	satisfactory	1	3.2			1	2.9
	Year 3*	**29**		**2**		**31**	
	very good	6	20.7	1	50.0	7	22.6
	good	21	72.4	1	50.0	22	71.0
	satisfactory	2	6.9			2	6.5
	Year 4*	**15**		**1**		**16**	
	very good	1	6.7			1	6.3
	good	13	86.7	1	100.0	14	87.5
	satisfactory	1	6.7			1	6.3
	Year 5*	**7**		**1**		**8**	
	very good	1	14.3			1	12.5
	good	5	71.4	1	100.0	6	75.0
	satisfactory	1	14.3			1	12.5

Source: Appendix Table 14.6.5.3

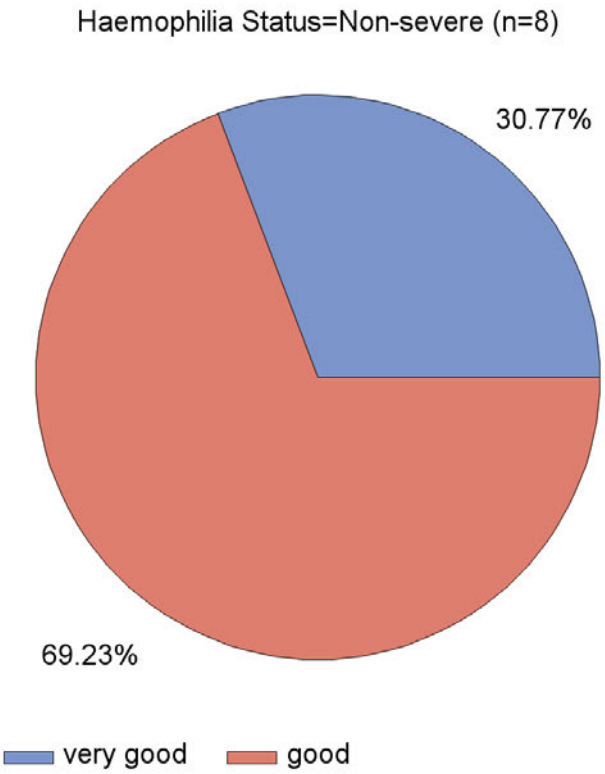
N = number in analysis population, n = number of patients with event / in category, SAF = Safety Analysis Set.

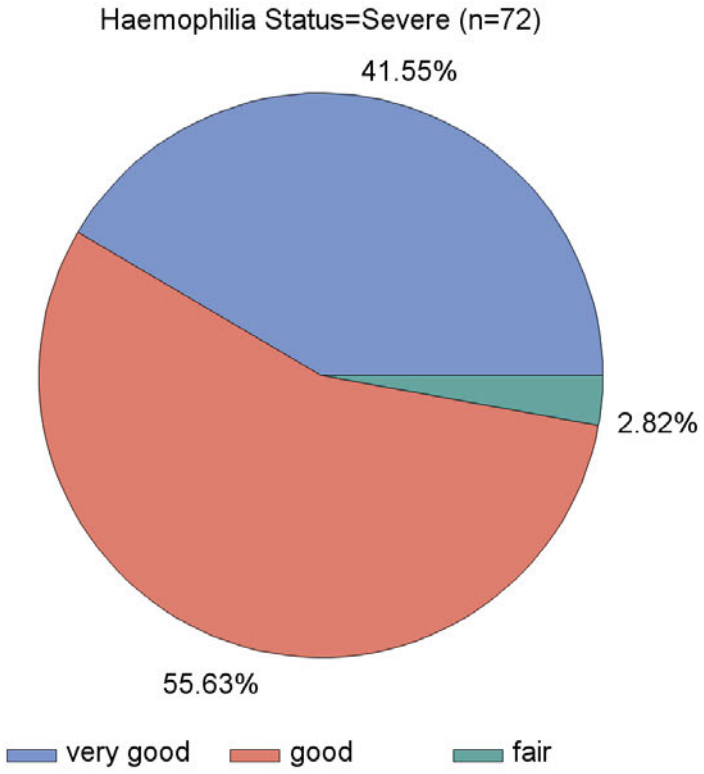
* End of year documentation.

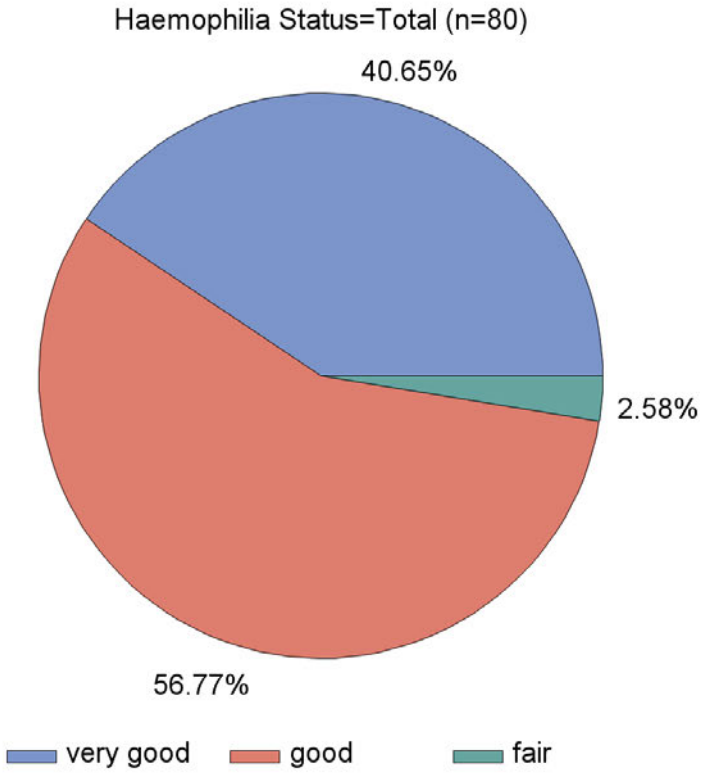
Treatment effectiveness, tolerance and handling of Haemoctin SDH assessed by the investigator (SAF and subgroups by hemophilia status) are displayed in Figure 3(a-c) as pie charts with percentages based on non-missing values from all available questionnaires. The diagrams visualize the predominant rating as “very good” or “good” in the subgroups by hemophilia status, i.e., “Non-severe” (N=8) and “Severe” (N=72), and the SAF (N=80).

Figure 3 Assessment of treatment effectiveness, tolerance and handling of Haemoctin SDH by the investigator (SAF and subgroups by hemophilia status)

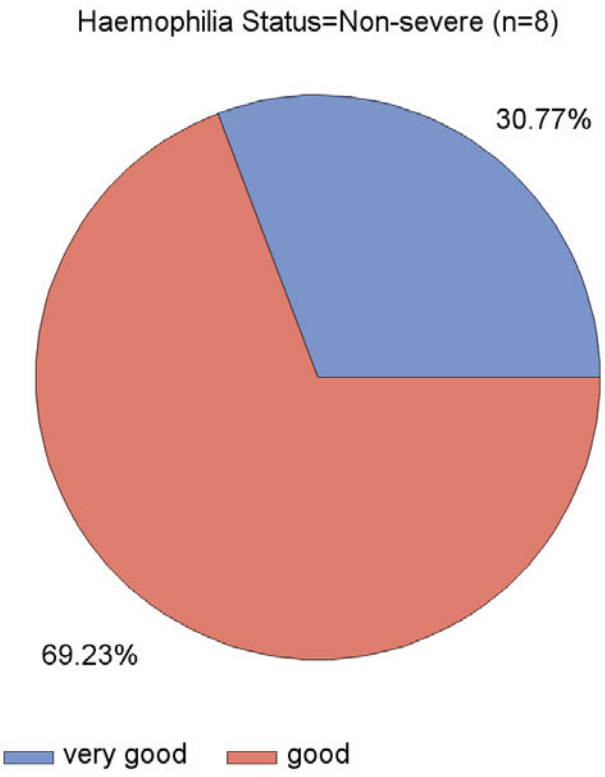
(a) Effectiveness (Investigators)

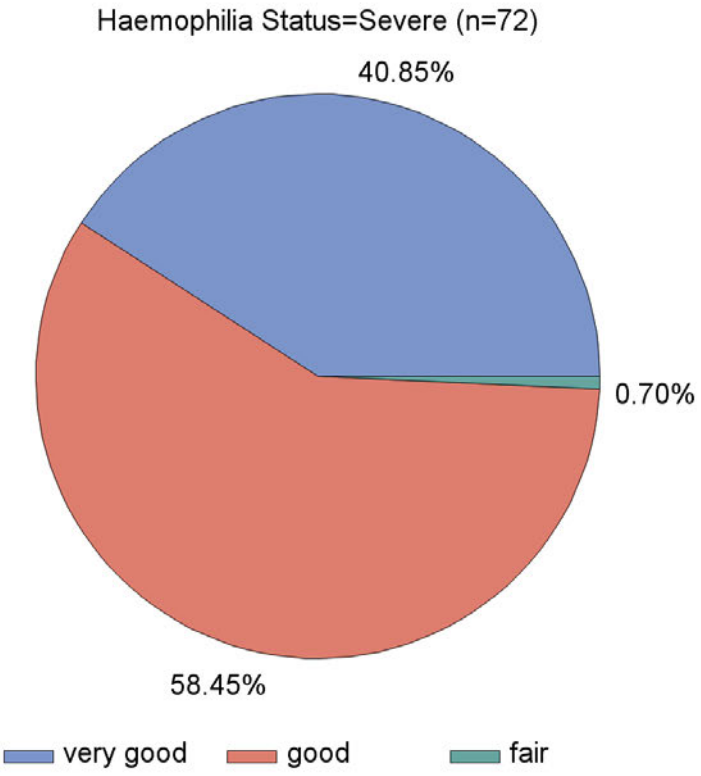


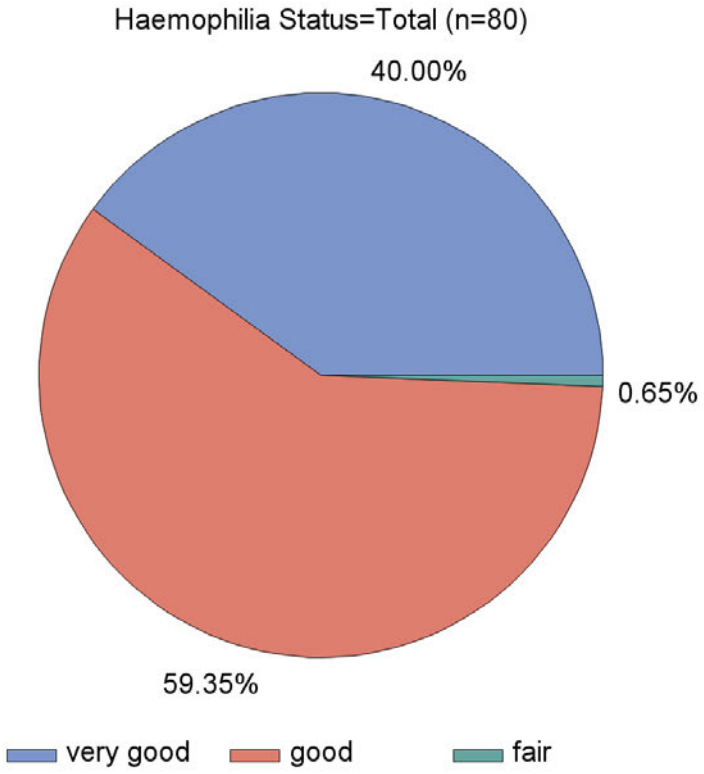

Haemophilia Status=Severe (n=72)
41.55%
2.82%
55.63%
very good
good
fair


Haemophilia Status=Total (n=80)
40.65%
2.58%
56.77%
very good
good
fair

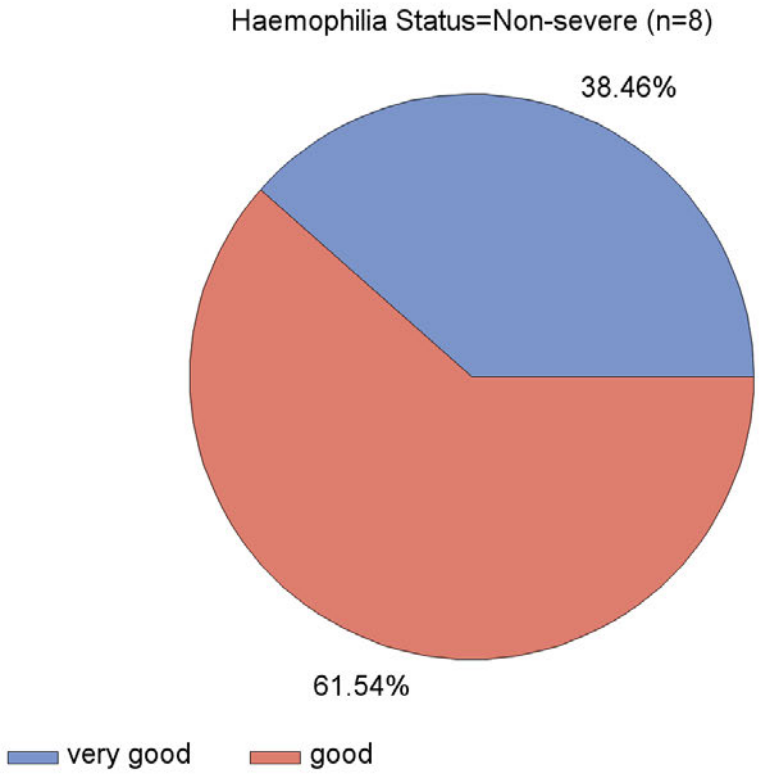
(b) Tolerance (Investigators)

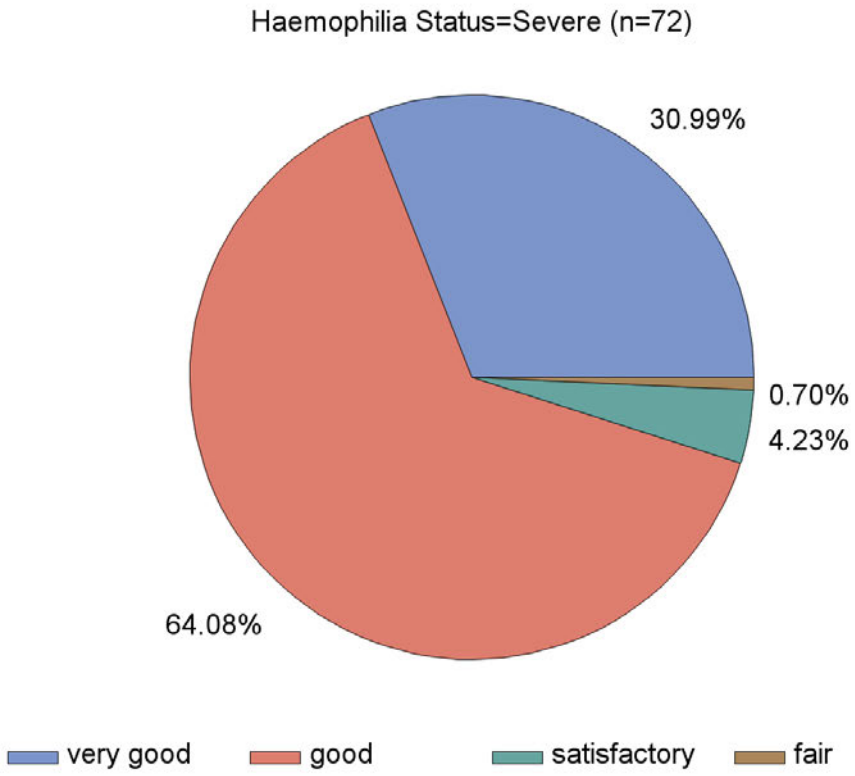


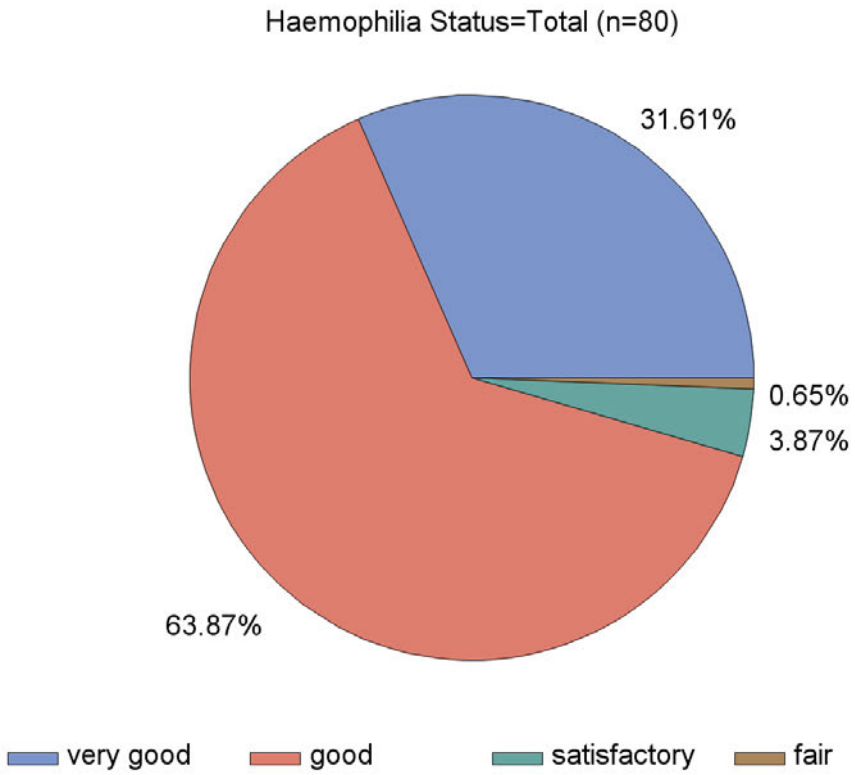




(c) Handling (Investigators)







Source: Appendix Figure 14.8.4

n = number of patients with event / within category, SAF = Safety Analysis Set.

Percentages are based on non-missing values from all available questionnaires. Not all patients have filled a questionnaire at every study visit.

12.5.6.2 Patients' Assessment of Treatment Effectiveness, Tolerance, Handling of Haemoctin SDH and Overall Condition

Similar to the investigators' assessment, the patients' assessment of treatment effectiveness, tolerance and handling of Haemoctin SDH for the SAF was predominantly "very good" or "good" at every end of year documentation. Less good effectiveness ratings were "fair" in only 0-3 patients per year. Less good tolerance ratings were "fair" in only 0-1 patients per year and "poor" in 1 patient at Year 1. Less good handling ratings were "satisfactory" in 1-3 patients per year and "fair" in 0-1 patient per year (Table 33).

Likewise, the patients' assessment of the overall condition for the SAF was predominantly "very good" or "good" at every end of year documentation. Less good ratings of the overall condition were "fair" in only 1-14 patients per year and "poor" in 1 patient in Year 1 (Table 33).

Results for SAF subgroups by treatment regimen are shown in Appendix Table 14.6.6.3.1. Results for the PSAF and corresponding subgroups by treatment regimen are shown in Appendix Table 14.6.6.2 and Table 14.6.6.2.1. Results for the FAS and corresponding subgroups by treatment regimen are shown in Appendix Table 14.6.6.1 and Table 14.6.6.1.1.

Table 33 Assessment of treatment effectiveness, tolerance and handling of Haemoctin SDH by the patient (SAF)

Evaluation of	Visit Evaluation by the patient	Hemophilia status					
		Severe (N=72)		Non-severe (N=8)		Total (N=80)	
		n	%	n	%	n	%
Effectiveness	**Year 1***	**55**		**4**		**59**	
	very good	29	52.7	2	50.0	31	52.5
	good	23	41.8	2	50.0	25	42.4
	fair	3	5.5			3	5.1
	Year 2*	**29**		**3**		**32**	
	very good	15	51.7			15	46.9
	good	11	37.9	3	100.0	14	43.8
	fair	3	10.3			3	9.4
	Year 3*	**27**		**1**		**28**	
	very good	17	63.0			17	60.7
	good	8	29.6	1	100.0	9	32.1
	fair	2	7.4			2	7.1
	Year 4*	**10**				**10**	
	very good	4	40.0			4	40.0
	good	6	60.0			6	60.0
	Year 5*	**7**		**1**		**8**	
	very good	2	28.6	1	100.0	3	37.5
	good	5	71.4			5	62.5

Evaluation of	Visit Evaluation by the patient	Hemophilia status					
		Severe (N=72)		Non-severe (N=8)		Total (N=80)	
		n	%	n	%	n	%
Tolerance	**Year 1***	**55**		**4**		**59**	
	very good	27	49.1	3	75.0	30	50.8
	good	26	47.3	1	25.0	27	45.8
	fair	1	1.8			1	1.7
	poor	1	1.8			1	1.7
	Year 2*	**29**		**3**		**32**	
	very good	17	58.6	1	33.3	18	56.3
	good	11	37.9	2	66.7	13	40.6
	fair	1	3.4			1	3.1
	Year 3*	**27**		**1**		**28**	
	very good	18	66.7			18	64.3
	good	8	29.6	1	100.0	9	32.1
	fair	1	3.7			1	3.6
	Year 4*	**10**				**10**	
	very good	4	40.0			4	40.0
	good	6	60.0			6	60.0
	Year 5*	**7**		**1**		**8**	
	very good	2	28.6	1	100.0	3	37.5
	good	5	71.4			5	62.5
Handling	**Year 1***	**55**		**4**		**59**	
	very good	21	38.2	3	75.0	24	40.7
	good	30	54.5	1	25.0	31	52.5
	satisfactory	3	5.5			3	5.1
	fair	1	1.8			1	1.7
	Year 2*	**29**		**3**		**32**	
	very good	11	37.9			11	34.4
	good	15	51.7	2	66.7	17	53.1
	satisfactory	2	6.9	1	33.3	3	9.4
	fair	1	3.4			1	3.1
	Year 3*	**27**		**1**		**28**	
	very good	8	29.6			8	28.6
	good	16	59.3	1	100.0	17	60.7
	satisfactory	3	11.1			3	10.7
	Year 4*	**10**				**10**	
	very good	2	20.0			2	20.0
	good	7	70.0			7	70.0
	satisfactory	1	10.0			1	10.0
	Year 5*	**7**		**1**		**8**	
	very good	1	14.3			1	12.5
	good	5	71.4	1	100.0	6	75.0
	satisfactory	1	14.3			1	12.5

Evaluation of	Visit Evaluation by the patient	Hemophilia status					
		Severe (N=72)		Non-severe (N=8)		Total (N=80)	
		n	%	n	%	n	%
Overall condition	**Year 1***	55		4		59	
	very good	16	29.1	1	25.0	17	28.8
	good	25	45.5	2	50.0	27	45.8
	Fair	13	23.6	1	25.0	14	23.7
	poor	1	1.8			1	1.7
	Year 2*	29		3		32	
	very good	8	27.6	1	33.3	9	28.1
	good	13	44.8	2	66.7	15	46.9
	fair	8	27.6			8	25.0
	Year 3*	27		2		29	
	very good	12	44.4			12	41.4
	good	11	40.7	2	100.0	13	44.8
	fair	4	14.8			4	13.8
	Year 4*	10				10	
	very good	3	30.0			3	30.0
	good	5	50.0			5	50.0
	fair	2	20.0			2	20.0
	Year 5*	7		1		8	
	very good	1	14.3	1	100.0	2	25.0
	good	5	71.4			5	62.5
	fair	1	14.3			1	12.5

Source: Appendix Table 14.6.6.3

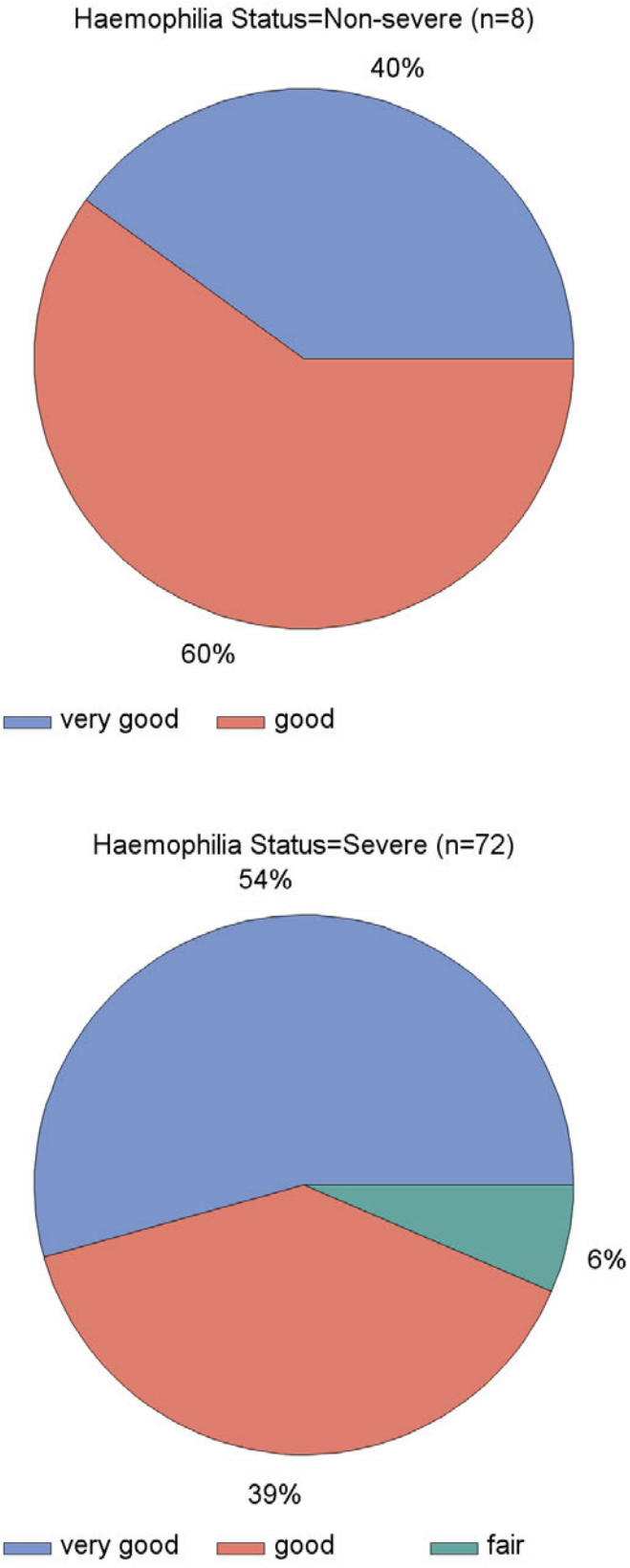
N = number in analysis population, n = number of patients with event / in category, SAF = Safety Analysis Set.

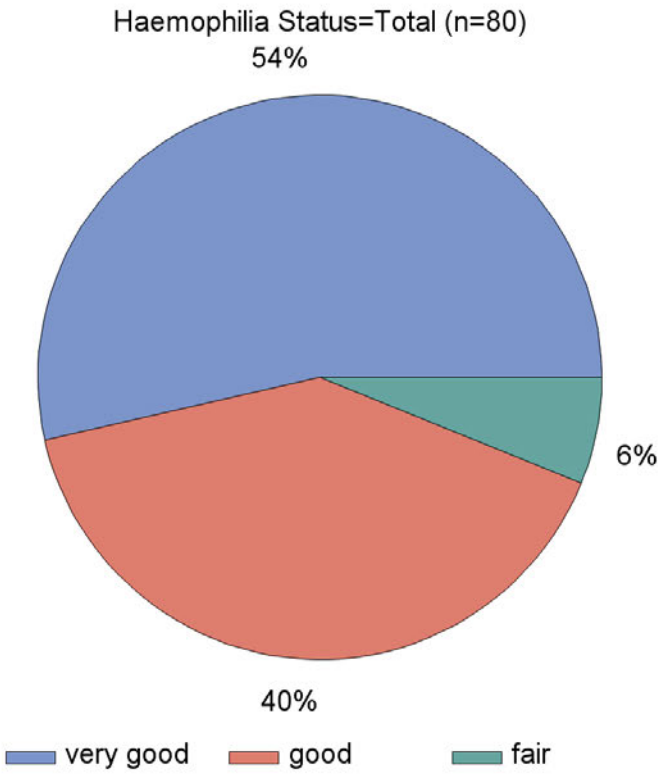
* End of year documentation.

Treatment effectiveness, tolerance, handling of Haemoctin SDH and overall condition assessed by the patient (SAF and subgroups by hemophilia status) are displayed in Figure 4(a-d) as pie charts with percentages based on non-missing values from all available questionnaires. The diagrams visualize the predominant rating as “very good” or “good” in the subgroups “Non-severe” (N=8) and “Severe” (N=72) and in the total SAF (N=80).

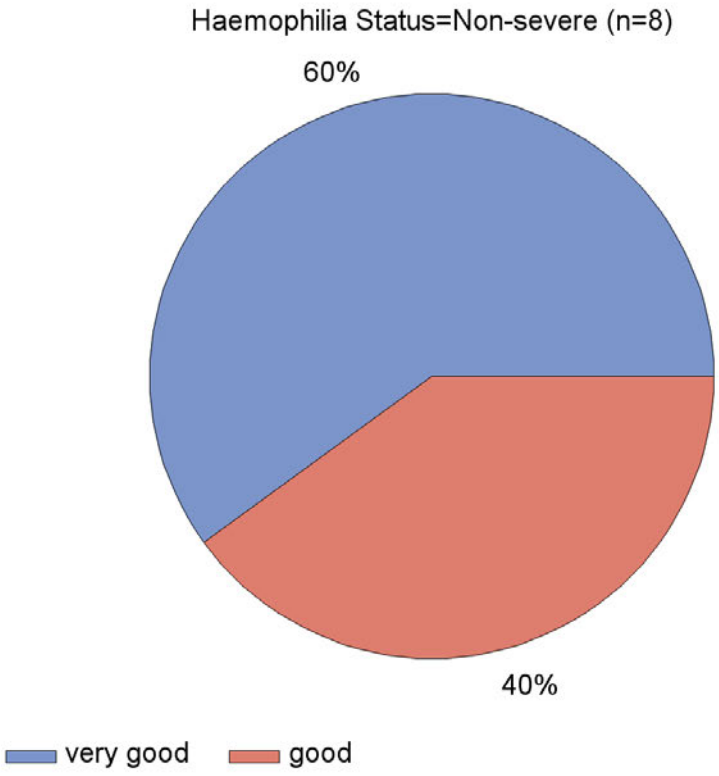
Figure 4 Assessment of treatment effectiveness, tolerance and handling of Haemoctin SDH by the investigator (SAF and subgroups by hemophilia status)

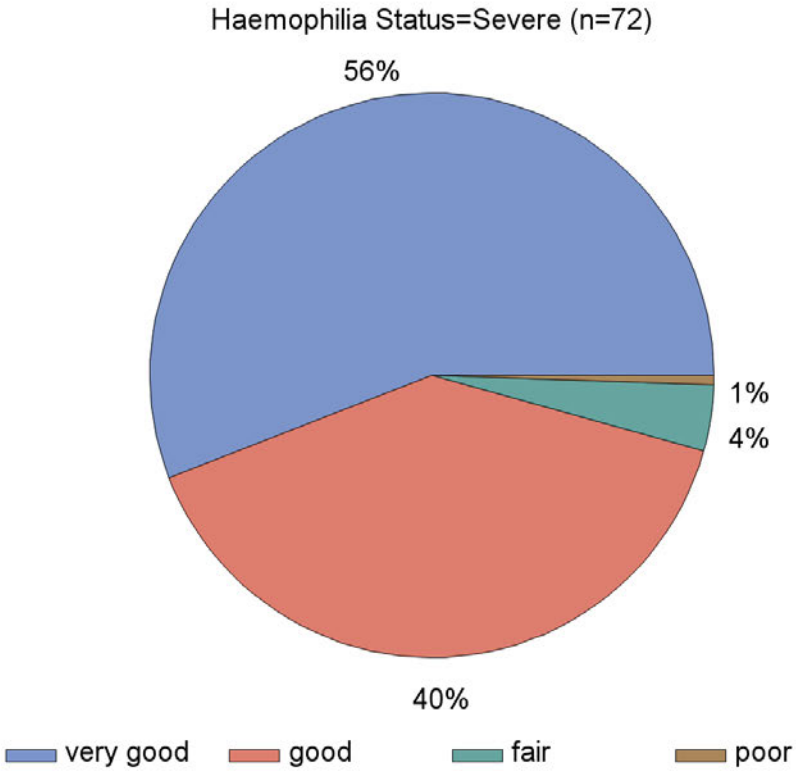
(a) Effectiveness (Patients)

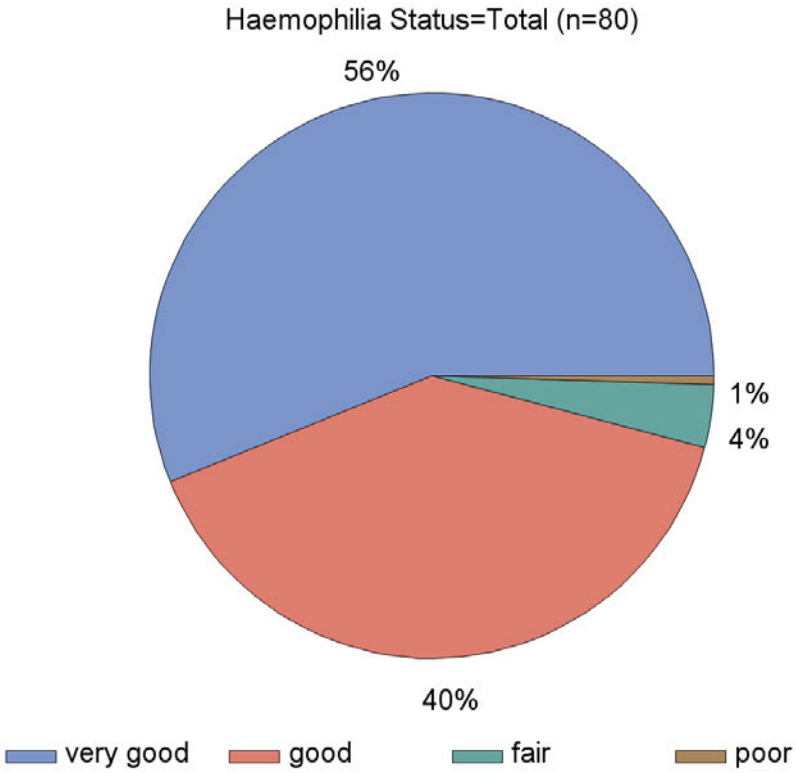




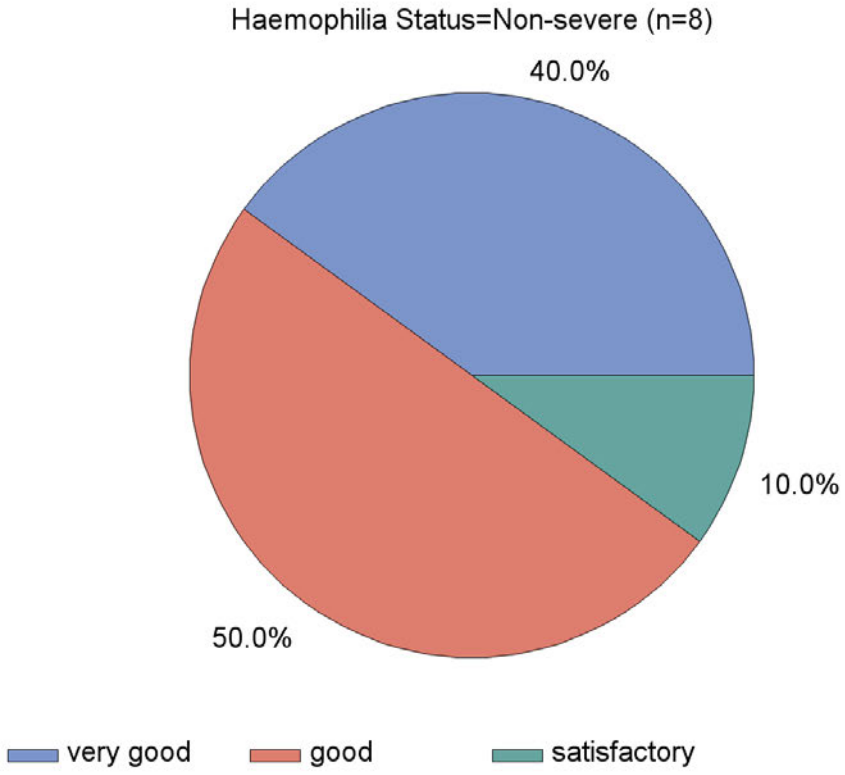
(b) Tolerance (Patients)

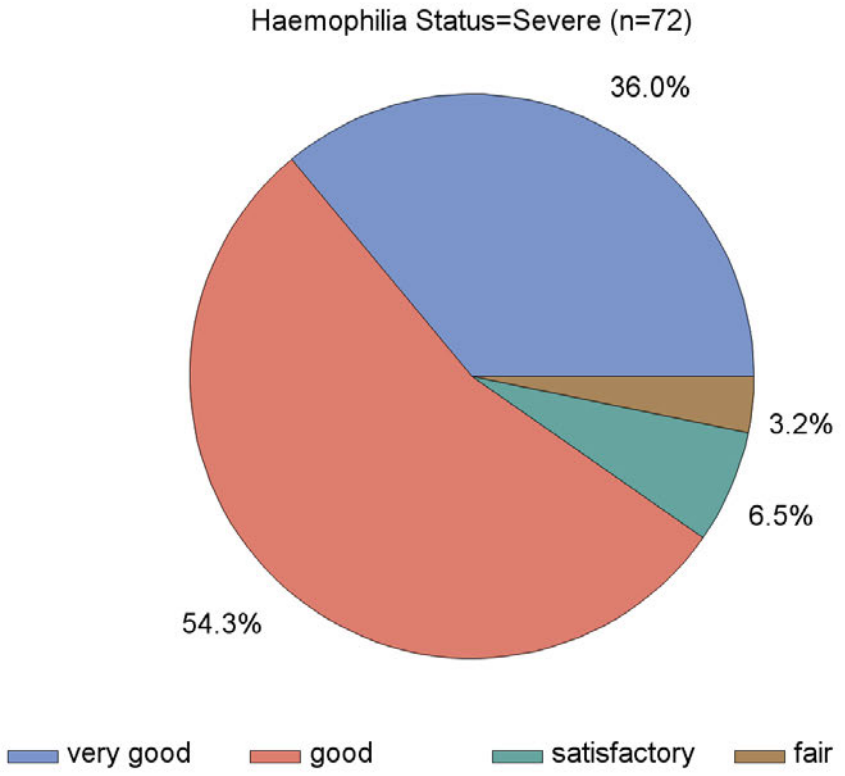


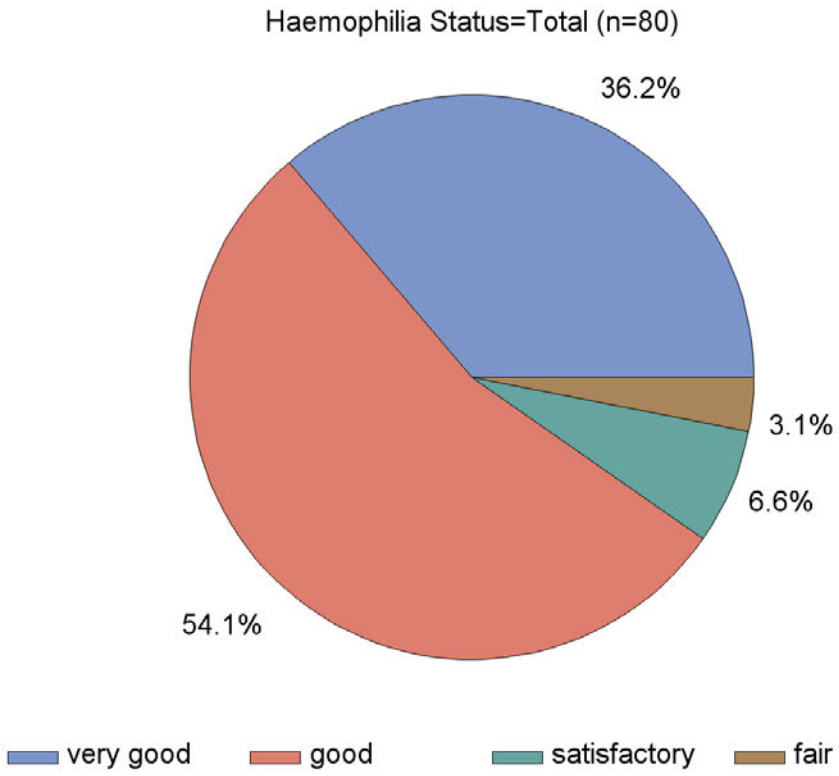

Haemophilia Status=Severe (n=72)
56%
1%
4%
40%
very good
good
fair
poor


Haemophilia Status=Total (n=80)
56%
1%
4%
40%
very good
good
fair
poor

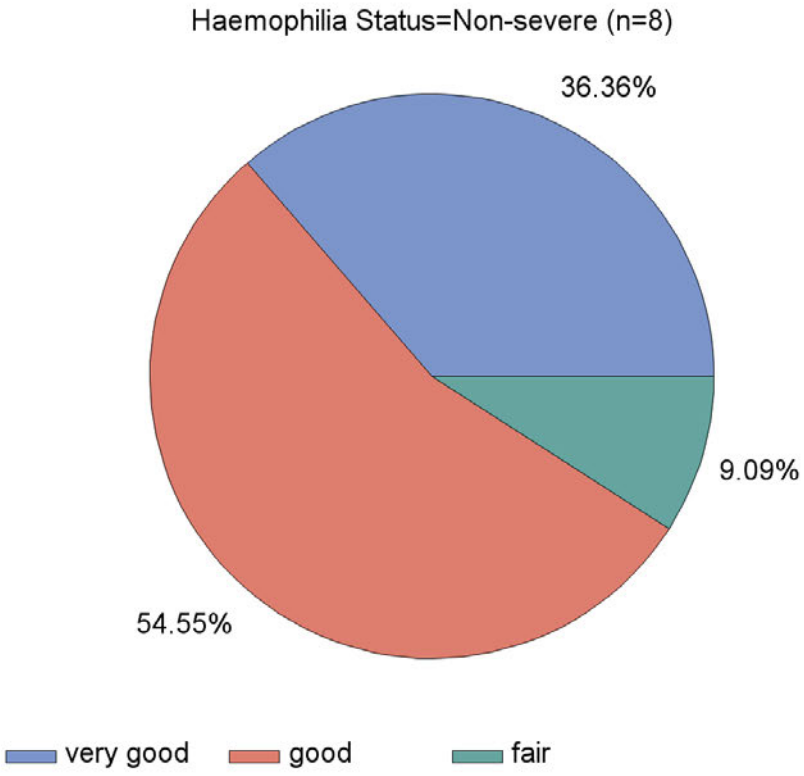
(c) Handling (Patients)

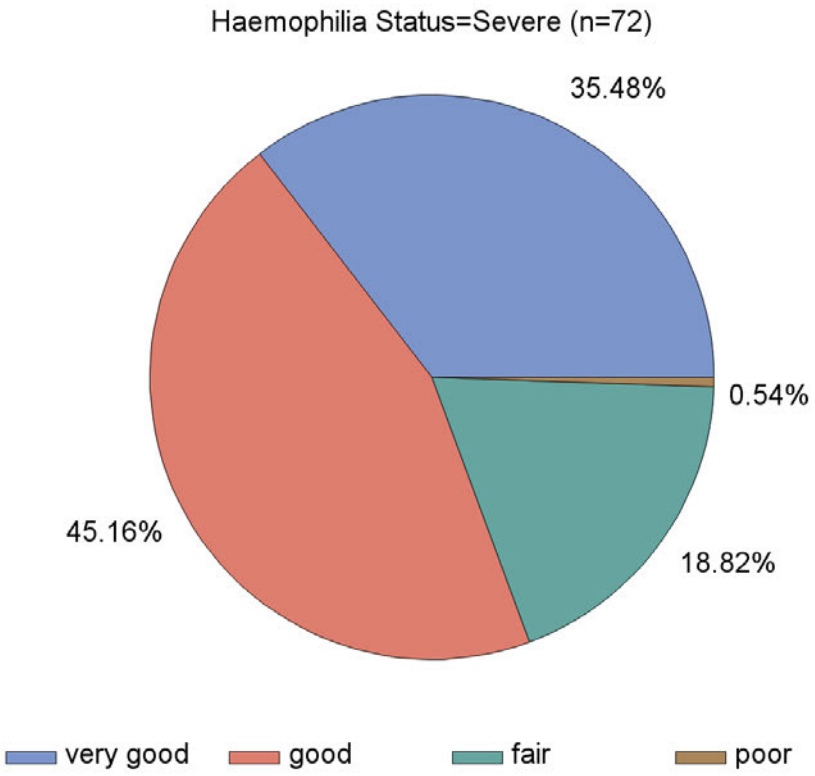


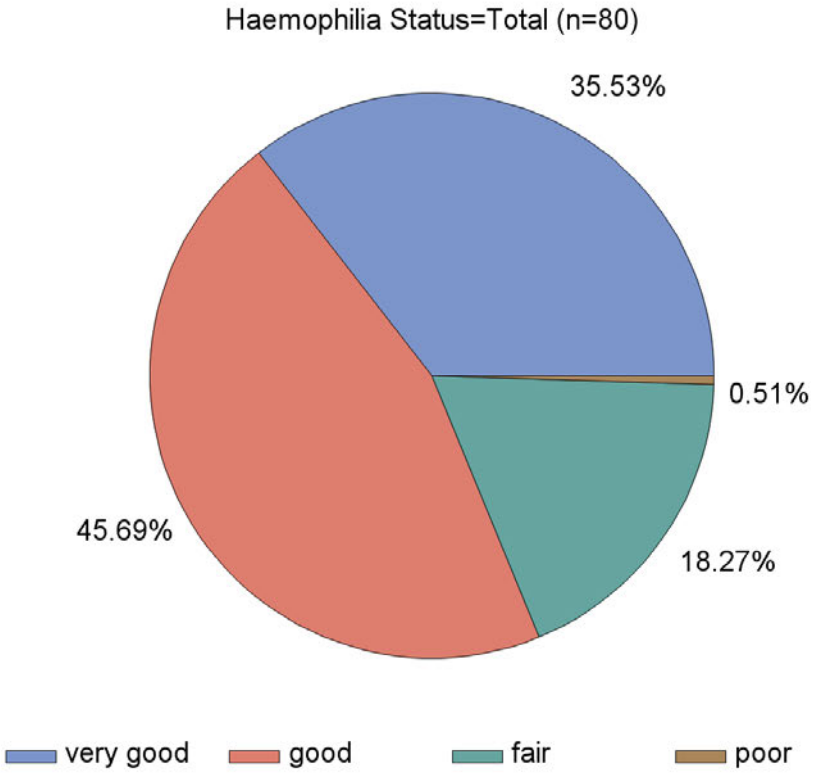




(d) Overall Condition (Patients)







Source: Appendix Figure 14.8.4

n = number of patients with event / within category, SAF = Safety Analysis Set.

Percentages are based on non-missing values from all available questionnaires. Not all patients have filled a questionnaire at every study visit.

12.5.6.3 Investigators' Assessment of Patients' Health

The investigators' assessment of the patients' health for the SAF was predominantly "very good" or "good" at every visit. Less good effectiveness ratings were "fair" in 9 (14.1%) patients at the follow-up 1. At all subsequent visits, the rating "fair" occurred in 0-2 patients (Table 34).

Results for SAF subgroups by treatment regimen are shown in Appendix Table 14.6.7.2.1. Results for the FAS and corresponding subgroups by treatment regimen are shown in Appendix Table 14.6.7.1 and Table 14.6.7.1.1.

Table 34 Assessment of patient's health by the investigator (SAF)

Evaluation of	Visit Evaluation by the investigator	Hemophilia status					
		Severe (N=72)		Non-severe (N=8)		Total (N=80)	
		n	%	n	%	n	%
Patient health	**Year 1, Follow-Up 1**	**60**		**4**		**64**	
	very good	24	40.0	1	25.0	25	39.1
	good	29	48.3	1	25.0	30	46.9
	fair	7	11.7	2	50.0	9	14.1
	Year 1, Follow-Up 2	**37**		**1**		**38**	
	very good	15	40.5			15	39.5
	good	20	54.1	1	100.0	21	55.3
	fair	2	5.4			2	5.3
	Year 1, Follow-Up 3	**23**				**23**	
	very good	12	52.2			12	52.2
	good	11	47.8			11	47.8
	Year 2, Follow-Up 1	**16**				**16**	
	very good	10	62.5			10	62.5
	good	5	31.3			5	31.3
	fair	1	6.3			1	6.3
	Year 2, Follow-Up 2	**8**				**8**	
	very good	6	75.0			6	75.0
	good	1	12.5			1	12.5
	fair	1	12.5			1	12.5
	Year 2, Follow-Up 3	**6**				**6**	
	very good	5	83.3			5	83.3
	good	1	16.7			1	16.7
	Year 2, Follow-Up 4	**2**				**2**	
	very good	1	50.0			1	50.0
	good	1	50.0			1	50.0
	Year 3, Follow-Up 1	**19**		**1**		**20**	
	very good	11	57.9			11	55.0
	good	7	36.8	1	100.0	8	40.0
	fair	1	5.3			1	5.0
	Year 3, Follow-Up 2	**9**				**9**	
	very good	4	44.4			4	44.4
	good	5	55.6			5	55.6

Evaluation of	Visit Evaluation by the investigator	Hemophilia status					
		Severe (N=72)		Non-severe (N=8)		Total (N=80)	
		n	%	n	%	n	%
Patient health	**Year 3, Follow-Up 3**	**8**				**8**	
	very good	3	37.5			3	37.5
	good	3	37.5			3	37.5
	fair	2	25.0			2	25.0
	Year 3, Follow-Up 4	**5**				**5**	
	very good	3	60.0			3	60.0
	good	2	40.0			2	40.0
	Year 4, Follow-Up 1	**12**				**12**	
	very good	5	41.7			5	41.7
	good	7	58.3			7	58.3
	Year 4, Follow-Up 2	**2**				**2**	
	very good	1	50.0			1	50.0
	fair	1	50.0			1	50.0
	Year 5, Follow-Up 1	**3**				**3**	
	good	2	66.7			2	66.7
	fair	1	33.3			1	33.3
	Year 5, Follow-Up 2	**1**				**1**	
	good	1	100.0			1	100.0
	Year 5, Follow-Up 3	**1**				**1**	
	good	1	100.0			1	100.0

Source: Appendix Table 14.6.7.2

N = number in analysis population, n = number of patients with event / in category, SAF = Safety Analysis Set.

12.5.7 Arthropathy Progress

An optional variable in this study was the arthropathy progress assessed with ultrasound and quantified with the hemophilia early arthropathy detection with ultrasound (HEAD-US) score. However, there were no observations pertaining to this variable (Appendix Table 14.6.8.1).

12.6 Adverse Events and Adverse Drug Reactions

The secondary objectives of this study aimed to assess the frequency, severity, seriousness and causality of AEs.

The primary data source for presenting and analyzing AEs is the clinical database, as detailed in Section 11.5. This approach ensures that the data and analyses are faithfully represented exactly as entered by investigators and site staff in the eCRF. Consequently, unless explicitly stated otherwise, the evaluation of seriousness and causal relationship is grounded in assessments made by the investigators. Additionally, the sponsor's supplementary data and analyses, where applicable and appropriate, have been incorporated and compared. Notably, special attention has been paid to the differences in coding between the clinical database and the global PV database.

The analyses further include differentiation based on various subgroups as defined in Section 11.9.2. AEs and SAEs are presented by patient in Appendix Listings 16.2.23.1 and 16.2.23.2, respectively.

All results presented in Sections 12.6.1 to 12.6.7 pertain to the SAF population, while the results in Sections 12.6.8 to 12.6.8.5 relate to the PSAF population.

12.6.1 Summary of Adverse Events

Overview summaries of AEs by category and hemophilia status reported in this study are provided in the Sections 12.6.1.1 to 12.6.1.5 for the total SAF population and by subgroups, severity and outcome.

12.6.1.1 Summary of Adverse Events in the Total SAF by Hemophilia A Status

An overall summary table of patients with AEs by category is provided in Table 35 for the SAF population.

In the total SAF, overall 913 AEs occurred in 59 (73.8%) patients. Of these, 893 AEs occurred in 52 (72.2%) patients of the “Severe” subgroup and 20 AEs in 7 (87.5%) patients of the “Non-severe” subgroup.

In the total SAF, 52 AEs in 23 (28.8%) patients were serious (SAEs). Of these, 47 SAEs occurred in 20 (27.8%) patients of the “Severe” subgroup and 5 SAEs in 3 (37.5%) patients of the “Non-severe” subgroup.

In the total SAF, 770 AESIs occurred in 49 (61.3%) patients. Of these, 761 AESIs occurred in 45 (62.5%) patients of the “Severe” subgroup and 9 AESIs in 4 (50.0%) patients of the “Non-severe” subgroup. In the total SAF, 5 AESIs in 5 (6.3%) patients were serious (SAESIs). Of these, 4 SAESIs occurred in 4 (5.6%) patients of the “Severe” subgroup and 1 SAESI in 1 (12.5%) patient of the “Non-severe” subgroup. In this summary, the term “AESI” refers to the definition in the observation plan, namely bleeding episodes, alongside the categories of thromboembolic events, hypersensitivity / anaphylactic reactions, development of anti-FVIII inhibitors and transmission of infective agents subsequently defined in the SAP (v1.0, 25-Jan-2023). The numbers shown here are a combination of all

these AE categories. In the detailed presentation below, the AE categories are presented separately. For the definition and further description of these AE categories, see Sections 12.6.4 and 12.6.5.

- Overall, 756 AESIs of the category of bleeding were reported in 48 (60.0%) patients. Of these, 747 AESIs occurred in 44 (61.1%) patients of the “Severe” subgroup and 9 AESIs in 4 (50.0%) patients of the “Non-severe” subgroup (Section 12.6.4.1).
- Overall, 4 AEs of the category of thromboembolic events were reported in 4 (5.0%) patients. All of these events occurred in 4 (5.6%) patients of the “Severe” subgroup, with no AEs reported in the “Non-severe” subgroup (Section 12.6.5.1).
- Overall, 10 AEs of the category of hypersensitivity / anaphylactic reactions were reported in 8 (10%) patients. All of these events occurred in 8 (11.1%) patients of the “Severe” subgroup, with no AEs reported in the “Non-severe” subgroup (Section 12.6.5.2).
- In the total SAF, no AEs of the categories of development of anti-FVIII inhibitor or transmission of infective agents were experienced by the patients (Sections 12.6.5.3 and 12.6.5.4).

None of the AEs were assessed by the investigators to be related to Haemoctin SDH. Therefore, no ADRs, no SADRs (including no related AESIs and no related SAESIs) were documented in the present study.

Four AEs in 1 (1.3%) patient belonging to the “Severe” subgroup of the total SAF resulted in death as it was not possible to ascertain which of the 4 events was the actual cause of death (Section 12.6.6). The investigator assessed all these 4 fatal AEs to be not related to Haemoctin SDH.

In the total SAF, 4 AEs in 4 (5.0%) patients led to discontinuation of Haemoctin SDH. Two of these AEs occurred in 2 (2.8%) patients of the “Severe” subgroup and 2 AEs in 2 (25.0%) patients of the “Non-severe” subgroup. The 4 AEs leading to discontinuation of Haemoctin SDH were judged by the investigators not to be related to Haemoctin SDH (Section 12.6.7).

Table 35 Summary of adverse events (SAF)

Type of AE	Hemophilia status								
	Severe (N=72)			Non-severe (N=8)			Total (N=80)		
	n	%	events	n	%	events	n	%	events
All Adverse events (AEs)	52	72.2	893	7	87.5	20	59	73.8	913
Serious adverse events (SAEs)	20	27.8	47	3	37.5	5	23	28.8	52
Adverse drug reactions (ADRs)	0	0.0	0	0	0.0	0	0	0.0	0
Serious adverse drug reactions (SADRs)	0	0.0	0	0	0.0	0	0	0.0	0
Adverse events of special interest (AESIs)*	45	62.5	761	4	50.0	9	49	61.3	770
Related Adverse events of special interest (Related AESIs)*	0	0.0	0	0	0.0	0	0	0.0	0
Serious adverse events of special interest (SAESIs)*	4	5.6	4	1	12.5	1	5	6.3	5
Related Serious adverse events of special interest (Related SAESIs)*	0	0.0	0	0	0.0	0	0	0.0	0
AEs resulting in death	1	1.4	4	0	0.0	0	1	1.3	4
AEs leading to discontinuation of Haemoctin SDH	2	2.8	2	2	25.0	2	4	5.0	4

Source: Appendix Table 14.5.1.1.1

N = number in analysis population, n = number of patients with event / in category, SAF = Safety Analysis Set.

* In this table, the term AESI refers to the definition in the observation plan, namely bleeding episodes, alongside the categories of thromboembolic events, hypersensitivity / anaphylactic reactions, development of anti-FVIII inhibitors and transmission of infective agents subsequently defined in the SAP (v1.0, 25-Jan-2023). The numbers shown here are a combination of all these AE categories. In the detailed presentation below, the AE categories are presented separately.

The total SAF (N=80) and the “Severe” subgroup (N=72) were largely identical leading to similar results. The “Non-severe” subgroup (N=8) was relatively small with larger divergence to the SAF (Table 35).

12.6.1.2 Summary of Adverse Events in SAF Subgroups by Treatment Regimen

An overall summary of patients with AEs by treatment regimen is provided in Table 36 for the SAF population.

In the subgroup “Prophylaxis” (N=75), 882 AEs occurred in 54 (72.0%) patients. The occurrence of all types of AEs was similar to the total SAF, which was expected due to the large overlap of patients between the two groups.

The proportion of patients with AEs of all AE categories was mostly higher in the smallest subgroup “Prophylaxis <20 IU/kg 3 times per week” (N=14) (394 AEs in 13 [92.9%] patients) and similarly high in the subgroup “Prophylaxis ≥20 IU/kg 3 times per week” (N=26) as in the subgroup “Prophylaxis” or the total SAF (105 AEs in 20 [76.9%] patients).

Table 36 Summary of adverse events in subgroups by treatment regimen (SAF)

Subgroup: Type of AE	Hemophilia status								
	Severe (N=72)			Non-severe (N=8)			Total (N=80)		
	n	%	events	n	%	events	n	%	events
Prophylaxis	(N=71)			(N=4)			(N=75)		
All Adverse events (AEs)	51	71.8	875	3	75.0	7	54	72.0	882
Serious adverse events (SAEs)	20	28.2	47	1	25.0	3	21	28.0	50
Adverse events of special interest (AESIs)*	44	62.0	745	2	50.0	2	46	61.3	747
Serious adverse events of special interest (SAESIs)*	4	5.6	4	1	25.0	1	5	6.7	5
AEs resulting in death	1	1.4	4	0	0.0	0	1	1.3	4
AEs leading to discontinuation of Haemoctin SDH	2	2.8	2	1	25.0	1	3	4.0	3
Prophylaxis <20 IU/kg 3 times per week	(N=12)			(N=2)			(N=14)		
All Adverse events (AEs)	12	100.0	393	1	50.0	1	13	92.9	394
Serious adverse events (SAEs)	6	50.0	18	0	0.0	0	6	42.9	18
Adverse events of special interest (AESIs)*	12	100.0	333	1	50.0	1	13	92.9	334
Serious adverse events of special interest (SAESIs)*	2	16.7	2	0	0.0	0	2	14.3	2
AEs resulting in death	0	0.0	0	0	0.0	0	0	0.0	0
AEs leading to discontinuation of Haemoctin SDH	1	8.3	1	0	0.0	0	1	7.1	1
Prophylaxis ≥20 IU/kg 3 times per week	(N=26)			(N=0)			(N=26)		
All Adverse events (AEs)	20	76.9	105				20	76.9	105
Serious adverse events (SAEs)	8	30.8	15				8	30.8	15
Adverse events of special interest (AESIs)*	15	57.7	73				15	57.7	73
Serious adverse events of special interest (SAESIs)*	1	3.8	1				1	3.8	1
AEs resulting in death	1	3.8	4				1	3.8	4
AEs leading to discontinuation of Haemoctin SDH	1	3.8	1				1	3.8	1

Source: Appendix Table 14.5.1.1.1.1

N = number in analysis population, n = number of patients with event / in category, SAF = Safety Analysis Set.

* In this table, the term AESI refers to the definition in the observation plan, namely bleeding episodes, alongside the categories of thromboembolic events, hypersensitivity / anaphylactic reactions, development of anti-FVIII inhibitors and transmission of infective agents subsequently defined in the SAP (v1.0, 25-Jan-2023). The numbers shown here are a combination of all these AE categories. In the detailed presentation below, the AE categories are presented separately.

No AEs were judged by the investigators to be related; therefore, the corresponding AE categories are omitted in this table.

12.6.1.3 Summary of Adverse Events in SAF Subgroups by Previous Treatment

An overall summary of AEs by previous treatment is shown in Table 37.

In the PTPs (N=65), 819 AEs occurred in 48 (73.8%) patients. The occurrence of all types of AEs was similar to the total SAF, which was expected due to the relatively large overlap of patients between the two groups. The proportion of patients with the various types of

AEs in the smaller subgroup of PUPs (N=13) tended to be mostly lower than in the subgroup of PTPs, particularly in the relatively low proportion of patients with AESIs in the total SAF (i.e., 46.2% of patients compared with 63.1% of patients in the PTPs and 61.3% of patients in the SAF).

Table 37 Summary of adverse events in subgroups by previous treatment (SAF)

Subgroup: Type of AE	Hemophilia status: Severe (N=72)			Non-severe (N=8)			Total (N=80)		
	n	%	events	n	%	events	n	%	events
PUPs	(N=11)			(N=2)			(N=13)		
All Adverse events (AEs)	7	63.6	77	2	100.0	5	9	69.2	82
Serious adverse events (SAEs)	2	18.2	2	1	50.0	1	3	23.1	3
Adverse events of special interest (AESIs)*	5	45.5	68	1	50.0	1	6	46.2	69
Serious adverse events of special interest (SAESIs)*	0	0.0	0	0	0.0	0	0	0.0	0
AEs resulting in death	0	0.0	0	0	0.0	0	0	0.0	0
AEs leading to discontinuation of Haemoctin SDH	0	0.0	0	0	0.0	0	0	0.0	0
PTPs	(N=60)			(N=5)			(N=65)		
All Adverse events (AEs)	44	73.3	808	4	80.0	11	48	73.8	819
Serious adverse events (SAEs)	18	30.0	45	1	20.0	1	19	29.2	46
Adverse events of special interest (AESIs)*	39	65.0	685	2	40.0	7	41	63.1	692
Serious adverse events of special interest (SAESIs)*	4	6.7	4	0	0.0	0	4	6.2	4
AEs resulting in death	1	1.7	4	0	0.0	0	1	1.5	4
AEs leading to discontinuation of Haemoctin SDH	2	3.3	2	1	20.0	1	3	4.6	3

Source: Appendix Table 14.5.1.1.1.2

N = number in analysis population, n = number of patients with event / in category, PTP = previously treated patient, PUP = previously untreated patient, SAF = Safety Analysis Set.

* In this table, the term AESI refers to the definition in the observation plan, namely bleeding episodes, alongside the categories of thromboembolic events, hypersensitivity / anaphylactic reactions, development of anti-FVIII inhibitors and transmission of infective agents subsequently defined in the SAP (v1.0, 25-Jan-2023). The numbers shown here are a combination of all these AE categories. In the detailed presentation below, the AE categories are presented separately.

No AEs were judged by the investigators to be related; therefore, the corresponding AE categories are omitted in this table.

12.6.1.4 Summary of Adverse Events by Severity

Among the overall 913 AEs in the total SAF, the majority was mild (666 AEs in 50 [62.5%] patients), followed by 173 moderate AEs in 34 (42.5%) patients and 28 severe AEs in 17 (21.3%) patients (severity not available for 46 AEs in 5 [6.3%] patients) (Table 38).

Table 38 Summary of adverse events by severity (SAF)

Severity of AE	Hemophilia status								
	Severe (N=72)			Non-severe (N=8)			Total (N=80)		
	n	%	events	n	%	events	n	%	events
Mild AEs	46	63.9	656	4	50.0	10	50	62.5	666
Moderate AEs	31	43.1	167	3	37.5	6	34	42.5	173
Severe AEs	15	20.8	24	2	25.0	4	17	21.3	28
Severity not available	5	6.9	46	0	0.0	0	5	6.3	46

Source: Appendix Table 14.5.1.2.1.2

AE = adverse event, N = number in analysis population, n = number of patients with event / in category, SAF = Safety Analysis Set.

12.6.1.5 Summary of Adverse Events by Outcome

Among the overall 913 AEs in the total SAF, the majority had the outcome “recovered/resolved” (814 AEs in 54 [67.5%] patients), followed by 17 AEs in 10 (12.5%) patients with the outcome “not recovered / not resolved”, 14 AEs in 10 (12.5%) patients with the outcome “recovering/resolving”, 9 AEs in 5 (6.3%) patients with the outcome “resolved with sequelae” and 4 fatal AEs in 1 (1.3%) patient. For 53 AEs in 10 [12.5%] patients the outcome was unknown and for 2 AEs in 2 [2.5%] patients it was not documented (Table 39).

Table 39 Summary of adverse events by outcome (SAF)

Outcome of AE	Hemophilia status								
	Severe (N=72)			Non-severe (N=8)			Total (N=80)		
	n	%	events	n	%	events	n	%	events
Recovered/resolved	47	65.3	796	7	87.5	18	54	67.5	814
Resolved with sequelae	5	6.9	9	0	0.0	0	5	6.3	9
Recovering/resolving	10	13.9	14	0	0.0	0	10	12.5	14
Fatal	1	1.4	4	0	0.0	0	1	1.3	4
Not recovered / not resolved	10	13.9	17	0	0.0	0	10	12.5	17
Unknown	8	11.1	51	2	25.0	2	10	12.5	53
Outcome not documented	2	2.8	2	0	0.0	0	2	2.5	2

Source: Appendix Table 14.5.1.2.1.3

AE = adverse event, N = number in analysis population, n = number of patients with event / in category, SAF = Safety Analysis Set.

12.6.2 Adverse Events by System Organ Class and Preferred Term

AEs are tabulated by SOC and PT in Appendix Table 14.5.1.2.1 and in Table 40.

The most frequently documented preferred terms (in ≥10% of patients in the total SAF) were “Haemarthrosis” (in 18 [22.5%] patients, 180 events; SOC “Musculoskeletal and connective tissue disorders”), “Spontaneous haemorrhage” (in 14 [17.5%] patients, 217 events; SOC “Blood and lymphatic system disorders”), “Haemorrhage” (in 13 [16.3%] patients, 282 events; SOC “Vascular disorders”), “Arthralgia” (in 9 [11.3%] patients, 12 events; SOC “Musculoskeletal and connective tissue disorders”) and “Traumatic haemorrhage” (in 9 [11.3%] patients, 15 events; SOC “Injury, poisoning and procedural complications”).

Table 40 Adverse events by system organ class and preferred term (SAF)

SYSTEM ORGAN CLASS preferred term	Hemophilia status								
	Severe (N=72)			Non-severe (N=8)			Total (N=80)		
	n	%	events	n	%	events	n	%	events
Patients with AEs	**52**	**72.2**	**893**	**7**	**87.5**	**20**	**59**	**73.8**	**913**
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	**23**	**31.9**	**225**	**4**	**50.0**	**4**	**27**	**33.8**	**229**
haemarthrosis	16	22.2	178	2	25.0	2	18	22.5	180
arthralgia	9	12.5	12	0	0.0	0	9	11.3	12
haemophilic arthropathy	5	6.9	7	0	0.0	0	5	6.3	7
muscle haemorrhage	5	6.9	6	0	0.0	0	5	6.3	6
osteoarthritis	4	5.6	4	0	0.0	0	4	5.0	4
arthropathy	2	2.8	2	0	0.0	0	2	2.5	2
joint swelling	2	2.8	2	0	0.0	0	2	2.5	2
muscle spasms	2	2.8	2	0	0.0	0	2	2.5	2
pain in extremity	2	2.8	3	0	0.0	0	2	2.5	3
synovitis	1	1.4	1	1	12.5	1	2	2.5	2
acquired claw toe	1	1.4	1	0	0.0	0	1	1.3	1
back pain	1	1.4	1	0	0.0	0	1	1.3	1
joint effusion	1	1.4	1	0	0.0	0	1	1.3	1
muscle atrophy	1	1.4	2	0	0.0	0	1	1.3	2
myosclerosis	1	1.4	1	0	0.0	0	1	1.3	1
soft tissue swelling	1	1.4	1	0	0.0	0	1	1.3	1
spinal stenosis	1	1.4	1	0	0.0	0	1	1.3	1
spondylolisthesis	0	0.0	0	1	12.5	1	1	1.3	1
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	**22**	**30.6**	**43**	**2**	**25.0**	**8**	**24**	**30.0**	**51**
traumatic haemorrhage	9	12.5	15	0	0.0	0	9	11.3	15
fall	6	8.3	12	0	0.0	0	6	7.5	12
contusion	2	2.8	2	1	12.5	2	3	3.8	4
joint injury	2	2.8	2	1	12.5	1	3	3.8	3
limb injury	1	1.4	2	1	12.5	4	2	2.5	6
wound	2	2.8	2	0	0.0	0	2	2.5	2
alcohol poisoning	1	1.4	1	0	0.0	0	1	1.3	1
bite	1	1.4	1	0	0.0	0	1	1.3	1
femoral neck fracture	1	1.4	1	0	0.0	0	1	1.3	1
head injury	1	1.4	1	0	0.0	0	1	1.3	1
incisional hernia	1	1.4	1	0	0.0	0	1	1.3	1

SYSTEM ORGAN CLASS preferred term	Hemophilia status								
	Severe (N=72)			Non-severe (N=8)			Total (N=80)		
	n	%	events	n	%	events	n	%	events
meniscus injury	0	0.0	0	1	12.5	1	1	1.3	1
periprosthetic fracture	1	1.4	1	0	0.0	0	1	1.3	1
post procedural myocardial infarction	1	1.4	1	0	0.0	0	1	1.3	1
radius fracture	1	1.4	1	0	0.0	0	1	1.3	1
VASCULAR DISORDERS	**19**	**26.4**	**294**	**1**	**12.5**	**1**	**20**	**25.0**	**295**
haemorrhage	12	16.7	281	1	12.5	1	13	16.3	282
haematoma	5	6.9	8	0	0.0	0	5	6.3	8
hypertension	3	4.2	3	0	0.0	0	3	3.8	3
peripheral venous disease	1	1.4	1	0	0.0	0	1	1.3	1
thrombophlebitis	1	1.4	1	0	0.0	0	1	1.3	1
INFECTIONS AND INFESTATIONS	**14**	**19.4**	**27**	**2**	**25.0**	**2**	**16**	**20.0**	**29**
tonsillitis	4	5.6	4	0	0.0	0	4	5.0	4
arthritis bacterial	2	2.8	2	0	0.0	0	2	2.5	2
covid-19	1	1.4	1	1	12.5	1	2	2.5	2
pneumonia	2	2.8	2	0	0.0	0	2	2.5	2
abscess	1	1.4	1	0	0.0	0	1	1.3	1
cellulitis	1	1.4	1	0	0.0	0	1	1.3	1
diverticulitis	1	1.4	1	0	0.0	0	1	1.3	1
ear infection	1	1.4	1	0	0.0	0	1	1.3	1
epididymitis	1	1.4	1	0	0.0	0	1	1.3	1
erysipelas	1	1.4	2	0	0.0	0	1	1.3	2
febrile infection	1	1.4	1	0	0.0	0	1	1.3	1
furuncle	1	1.4	1	0	0.0	0	1	1.3	1
gingivitis	1	1.4	1	0	0.0	0	1	1.3	1
infection	1	1.4	1	0	0.0	0	1	1.3	1
influenza	1	1.4	1	0	0.0	0	1	1.3	1
paronychia	1	1.4	1	0	0.0	0	1	1.3	1
periodontitis	1	1.4	1	0	0.0	0	1	1.3	1
pilonidal disease	0	0.0	0	1	12.5	1	1	1.3	1
upper respiratory tract infection	1	1.4	1	0	0.0	0	1	1.3	1
urinary tract infection	1	1.4	1	0	0.0	0	1	1.3	1
vascular device infection	1	1.4	1	0	0.0	0	1	1.3	1
viral infection	1	1.4	1	0	0.0	0	1	1.3	1
BLOOD AND LYMPHATIC SYSTEM DISORDERS	**15**	**20.8**	**218**	**0**	**0.0**	**0**	**15**	**18.8**	**218**
spontaneous haemorrhage	14	19.4	217	0	0.0	0	14	17.5	217
anaemia	1	1.4	1	0	0.0	0	1	1.3	1
GASTROINTESTINAL DISORDERS	**13**	**18.1**	**24**	**1**	**12.5**	**1**	**14**	**17.5**	**25**
dental caries	2	2.8	7	0	0.0	0	2	2.5	7
gingival bleeding	2	2.8	2	0	0.0	0	2	2.5	2
abdominal discomfort	1	1.4	1	0	0.0	0	1	1.3	1
abdominal hernia	1	1.4	1	0	0.0	0	1	1.3	1
barrett's oesophagus	1	1.4	1	0	0.0	0	1	1.3	1
dental discomfort	1	1.4	1	0	0.0	0	1	1.3	1
diarrhoea	1	1.4	1	0	0.0	0	1	1.3	1

SYSTEM ORGAN CLASS preferred term	Hemophilia status								
	Severe (N=72)			Non-severe (N=8)			Total (N=80)		
	n	%	events	n	%	events	n	%	events
gastritis	1	1.4	1	0	0.0	0	1	1.3	1
haematochezia	1	1.4	1	0	0.0	0	1	1.3	1
intra-abdominal haematoma	1	1.4	1	0	0.0	0	1	1.3	1
large intestine perforation	1	1.4	1	0	0.0	0	1	1.3	1
loose tooth	0	0.0	0	1	12.5	1	1	1.3	1
mouth haemorrhage	1	1.4	1	0	0.0	0	1	1.3	1
noninfective sialoadenitis	1	1.4	1	0	0.0	0	1	1.3	1
oral disorder	1	1.4	1	0	0.0	0	1	1.3	1
pancreatic disorder	1	1.4	1	0	0.0	0	1	1.3	1
toothache	1	1.4	1	0	0.0	0	1	1.3	1
umbilical hernia	1	1.4	1	0	0.0	0	1	1.3	1
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	**12**	**16.7**	**16**	**1**	**12.5**	**1**	**13**	**16.3**	**17**
general physical health deterioration	1	1.4	1	1	12.5	1	2	2.5	2
localised oedema	2	2.8	4	0	0.0	0	2	2.5	4
chest discomfort	1	1.4	1	0	0.0	0	1	1.3	1
gait disturbance	1	1.4	1	0	0.0	0	1	1.3	1
impaired healing	1	1.4	1	0	0.0	0	1	1.3	1
inflammation	1	1.4	1	0	0.0	0	1	1.3	1
malaise	1	1.4	1	0	0.0	0	1	1.3	1
mucosal haemorrhage	1	1.4	1	0	0.0	0	1	1.3	1
multiple organ dysfunction syndrome	1	1.4	1	0	0.0	0	1	1.3	1
peripheral swelling	1	1.4	1	0	0.0	0	1	1.3	1
pyrexia	1	1.4	2	0	0.0	0	1	1.3	2
swelling	1	1.4	1	0	0.0	0	1	1.3	1
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	**6**	**8.3**	**10**	**0**	**0.0**	**0**	**6**	**7.5**	**10**
epistaxis	3	4.2	6	0	0.0	0	3	3.8	6
cough	2	2.8	2	0	0.0	0	2	2.5	2
oropharyngeal pain	1	1.4	2	0	0.0	0	1	1.3	2
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	**5**	**6.9**	**9**	**0**	**0.0**	**0**	**5**	**6.3**	**9**
acne	1	1.4	1	0	0.0	0	1	1.3	1
dermatitis	1	1.4	1	0	0.0	0	1	1.3	1
nail bed bleeding	1	1.4	1	0	0.0	0	1	1.3	1
skin haemorrhage	1	1.4	4	0	0.0	0	1	1.3	4
skin ulcer	1	1.4	1	0	0.0	0	1	1.3	1
urticaria	1	1.4	1	0	0.0	0	1	1.3	1
CARDIAC DISORDERS	**3**	**4.2**	**3**	**0**	**0.0**	**0**	**3**	**3.8**	**3**
atrial fibrillation	2	2.8	2	0	0.0	0	2	2.5	2
stress cardiomyopathy	1	1.4	1	0	0.0	0	1	1.3	1
METABOLISM AND NUTRITION DISORDERS	**3**	**4.2**	**3**	**0**	**0.0**	**0**	**3**	**3.8**	**3**
hyperuricaemia	1	1.4	1	0	0.0	0	1	1.3	1
hypokalaemia	1	1.4	1	0	0.0	0	1	1.3	1
propofol infusion syndrome	1	1.4	1	0	0.0	0	1	1.3	1

SYSTEM ORGAN CLASS preferred term	Hemophilia status								
	Severe (N=72)			Non-severe (N=8)			Total (N=80)		
	n	%	events	n	%	events	n	%	events
NERVOUS SYSTEM DISORDERS	**3**	**4.2**	**3**	**0**	**0.0**	**0**	**3**	**3.8**	**3**
headache	1	1.4	1	0	0.0	0	1	1.3	1
paraparesis	1	1.4	1	0	0.0	0	1	1.3	1
status epilepticus	1	1.4	1	0	0.0	0	1	1.3	1
RENAL AND URINARY DISORDERS	**2**	**2.8**	**2**	**1**	**12.5**	**3**	**3**	**3.8**	**5**
haematuria	2	2.8	2	1	12.5	1	3	3.8	3
pollakiuria	0	0.0	0	1	12.5	1	1	1.3	1
urinary retention	0	0.0	0	1	12.5	1	1	1.3	1
SURGICAL AND MEDICAL PROCEDURES	**3**	**4.2**	**3**	**0**	**0.0**	**0**	**3**	**3.8**	**3**
arteriovenous fistula operation	2	2.8	2	0	0.0	0	2	2.5	2
wisdom teeth removal	1	1.4	1	0	0.0	0	1	1.3	1
CONGENITAL, FAMILIAL AND GENETIC DISORDERS	**2**	**2.8**	**2**	**0**	**0.0**	**0**	**2**	**2.5**	**2**
factor ii mutation	2	2.8	2	0	0.0	0	2	2.5	2
EYE DISORDERS	**2**	**2.8**	**6**	**0**	**0.0**	**0**	**2**	**2.5**	**6**
conjunctival haemorrhage	1	1.4	4	0	0.0	0	1	1.3	4
eye haemorrhage	1	1.4	1	0	0.0	0	1	1.3	1
retinopathy hypertensive	1	1.4	1	0	0.0	0	1	1.3	1
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	**2**	**2.8**	**2**	**0**	**0.0**	**0**	**2**	**2.5**	**2**
hepatocellular carcinoma	1	1.4	1	0	0.0	0	1	1.3	1
melanocytic naevus	1	1.4	1	0	0.0	0	1	1.3	1
INVESTIGATIONS	**1**	**1.4**	**1**	**0**	**0.0**	**0**	**1**	**1.3**	**1**
weight decreased	1	1.4	1	0	0.0	0	1	1.3	1
PSYCHIATRIC DISORDERS	**1**	**1.4**	**1**	**0**	**0.0**	**0**	**1**	**1.3**	**1**
depression	1	1.4	1	0	0.0	0	1	1.3	1
REPRODUCTIVE SYSTEM AND BREAST DISORDERS	**1**	**1.4**	**1**	**0**	**0.0**	**0**	**1**	**1.3**	**1**
benign prostatic hyperplasia	1	1.4	1	0	0.0	0	1	1.3	1

Source: Appendix Table 14.5.1.2.1

AE = adverse event, MedDRA = Medical Dictionary for Regulatory Activities, N = number in analysis population, n = number of patients with event / in category, SAF = Safety Analysis Set.

AEs were coded using MedDRA version 25.1.

12.6.2.1 Most Frequently Reported Adverse Events

While Table 40 shows all AEs, Table 41 shows only those preferred terms with an incidence of ≥5% in the “Severe” or “Non-severe” subgroup.

By SOC, most patients had AEs related to the following: ”Musculoskeletal and connective tissue disorders” (27 [33.8%] patients, 229 events; 225 events in 23 [31.9%] patients in the severe and 2 events in 2 [50%] patients in the non-severe subgroup), ”Injury, poisoning and procedural complications” (24 [30.0%] patients, 51 events; 43 events in 22 [30.6%]

patients in the severe and 8 events in 2 [25.0%] patients in the non-severe subgroup) and “Vascular disorders” (20 [25.0%] patients, 295 events; 294 events in 19 [26.4%] patients in the severe and 1 event in 1 [12.5%] patient in the non-severe subgroup). The frequency of these SOCs suggests a correlation with the underlying disease.

By PT, the most commonly reported AEs were “Haemarthrosis” (18 [22.5%] patients, 180 events; 178 events in 16 [22.2%] patients in the severe and 2 events in 2 [25.0%] patients in the non-severe subgroup), “Spontaneous haemorrhage” (14 [17.5%] patients, 217 events; 217 events in 14 [19.4%] patients in the severe and 0 events in the non-severe subgroup) and “Haemorrhage” (13 [16.3%] patients, 282 events; 281 events in 12 [16.7%] patients in the severe and 1 event in 1 [12.5%] patients in the non-severe subgroup). The frequency of these PTs suggests a correlation with the underlying disease.

Table 41 Adverse events by system organ class and preferred term in ≥5% of patients in the "Severe" or "Non-severe" subgroup at the preferred term level (SAF)

SYSTEM ORGAN CLASS preferred term	Hemophilia status								
	Severe (N=72)			Non-severe (N=8)			Total (N=80)		
	n	%	events	n	%	events	n	%	events
Patients with AEs	**52**	**72.2**	**893**	**7**	**87.5**	**20**	**59**	**73.8**	**913**
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	**23**	**31.9**	**225**	**4**	**50.0**	**4**	**27**	**33.8**	**229**
haemarthrosis	16	22.2	178	2	25.0	2	18	22.5	180
arthralgia	9	12.5	12	0	0.0	0	9	11.3	12
haemophilic arthropathy	5	6.9	7	0	0.0	0	5	6.3	7
muscle haemorrhage	5	6.9	6	0	0.0	0	5	6.3	6
osteoarthritis	4	5.6	4	0	0.0	0	4	5.0	4
synovitis	1	1.4	1	1	12.5	1	2	2.5	2
spondylolisthesis	0	0.0	0	1	12.5	1	1	1.3	1
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	**22**	**30.6**	**43**	**2**	**25.0**	**8**	**24**	**30.0**	**51**
traumatic haemorrhage	9	12.5	15	0	0.0	0	9	11.3	15
fall	6	8.3	12	0	0.0	0	6	7.5	12
contusion	2	2.8	2	1	12.5	2	3	3.8	4
joint injury	2	2.8	2	1	12.5	1	3	3.8	3
limb injury	1	1.4	2	1	12.5	4	2	2.5	6
meniscus injury	0	0.0	0	1	12.5	1	1	1.3	1
VASCULAR DISORDERS	**19**	**26.4**	**294**	**1**	**12.5**	**1**	**20**	**25.0**	**295**
haemorrhage	12	16.7	281	1	12.5	1	13	16.3	282
haematoma	5	6.9	8	0	0.0	0	5	6.3	8
INFECTIONS AND INFESTATIONS	**14**	**19.4**	**27**	**2**	**25.0**	**2**	**16**	**20.0**	**29**
tonsillitis	4	5.6	4	0	0.0	0	4	5.0	4
covid-19	1	1.4	1	1	12.5	1	2	2.5	2
pilonidal disease	0	0.0	0	1	12.5	1	1	1.3	1
BLOOD AND LYMPHATIC SYSTEM DISORDERS	**15**	**20.8**	**218**	**0**	**0.0**	**0**	**15**	**18.8**	**218**
spontaneous haemorrhage	14	19.4	217	0	0.0	0	14	17.5	217
GASTROINTESTINAL DISORDERS	**13**	**18.1**	**24**	**1**	**12.5**	**1**	**14**	**17.5**	**25**
loose tooth	0	0.0	0	1	12.5	1	1	1.3	1
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	**12**	**16.7**	**16**	**1**	**12.5**	**1**	**13**	**16.3**	**17**
general physical health deterioration	1	1.4	1	1	12.5	1	2	2.5	2
RENAL AND URINARY DISORDERS	**2**	**2.8**	**2**	**1**	**12.5**	**3**	**3**	**3.8**	**5**
haematuria	2	2.8	2	1	12.5	1	3	3.8	3
pollakiuria	0	0.0	0	1	12.5	1	1	1.3	1
urinary retention	0	0.0	0	1	12.5	1	1	1.3	1

Source: Appendix Table 14.5.1.2.1

AE = adverse event, MedDRA = Medical Dictionary for Regulatory Activities, N = number in analysis population, n = number of patients with event / in category, SAF = Safety Analysis Set.

AEs were coded using MedDRA version 25.1.

12.6.2.2 Adverse Events by Treatment Regimen

AEs in SAF subgroups by treatment regimen are shown in Appendix Table 14.5.1.2.1.1.

In patients on “Prophylaxis <20 IU/kg 3 times per week” (N=14), the most commonly reported AEs were “Haemarthrosis” (8 [57.1%] patients, 131 events), “Haemorrhage” (8 [57.1%] patients, 170 events and “Arthralgia” (6 [42.9%] patients, 8 events).

In patients on “Prophylaxis ≥20 IU/kg 3 times per week” (N=26), the most commonly reported AEs were “Traumatic haemorrhage” (5 [19.2%] patients, 6 events), “Haemarthrosis” (4 [15.4%] patients, 23 events and “Spontaneous haemorrhage” (4 [15.4%] patients, 16 events).

The comparison of the subgroups is problematic due to the imbalance in the numbers of patients (Section 13.2). However, in consideration of the prophylaxis regimen of “≥20 IU/kg 3 times per week” recommended in the SmPC of Haemoctin SDH, it was anticipated that a higher number of bleeding events related to the underlying disease would occur in patients undergoing a prophylaxis regimen of “<20 IU/kg 3 times per week”.

12.6.2.3 Adverse Events in the Global PV Database

As outlined in Section 11.5, two separate systems were utilized for capturing data on AEs, the clinical database and the global PV database. The coding of AEs, previous and concomitant diseases was performed both in the clinical database and the global PV database (see Section 11.8). In the clinical database, coding was done precisely according to the reported verbatim, whereas in the global PV database, significant emphasis was placed on capturing the exact medical context based on additional information provided or obtained. This resulted in discrepancies, especially in the area of coded AEs, which, however, had no impact on the safety analyses.

This section aims to delineate observed differences between the two systems.

Most differences can be seen in the coding of bleeding events. While in the clinical database the MedDRA PTs ”Haemorrhages” (282 vs. 42 events) and ”Spontaneous haemorrhages” (217 vs. 49 events) have mainly been used, the term ”Haemarthrosis” prevails in the global PV database (568 vs. 180 events).

Similarly, there are differences in the assessment of seriousness. While the clinical database precisely reflects the investigators’ seriousness assessment, Biotest has taken a more conservative approach resulting in a different number of SAEs in the two databases (52 SAEs in the clinical database and 178 SAEs in the global PV database).

Sections 12.6.3.3 and 12.6.4.3 provide a tabular side-by-side comparison of both SAEs and AESIs from both systems.

A complete summary tabulation encompassing all AEs by SOC and PT from the global PV database is presented in Appendix 2 (Section 17.2).

12.6.3 Serious Adverse Events by System Organ Class and Preferred Term

SAEs are tabulated by SOC and PT in Appendix Table 14.5.1.3.1 and in Table 42.

The most frequently documented preferred terms (in ≥2% of patients in the total SAF) were "Haemophilic arthropathy" (in 3 [3.8%] patients, 4 events; SOC "Musculoskeletal and connective tissue disorders"), "Osteoarthritis" (in 2 [2.5%] patients, 2 events; SOC "Musculoskeletal and connective tissue disorders") and "Arthritis bacterial" (in 2 [2.5%] patients, 2 events; SOC "Infections and infestations"). All other SAEs were single preferred terms in single patients.

Severity of SAEs is shown in Appendix Table 14.5.1.3.1. For "Haemophilic arthropathy",3 events were moderate and 1 event severe, for "Osteoarthritis" both events were severe and for "Arthritis bacterial" 1 event was moderate and 1 event severe.

Table 42 Serious adverse events by system organ class and preferred term (SAF)

SYSTEM ORGAN CLASS preferred term	Hemophilia status								
	Severe (N=72)			Non-severe (N=8)			Total (N=80)		
	n	%	events	n	%	events	n	%	events
Patients with SAEs	**20**	**27.8**	**47**	**3**	**37.5**	**5**	**23**	**28.8**	**52**
INFECTIONS AND INFESTATIONS	**7**	**9.7**	**9**	**0**	**0.0**	**0**	**7**	**8.8**	**9**
arthritis bacterial	2	2.8	2	0	0.0	0	2	2.5	2
cellulitis	1	1.4	1	0	0.0	0	1	1.3	1
diverticulitis	1	1.4	1	0	0.0	0	1	1.3	1
epididymitis	1	1.4	1	0	0.0	0	1	1.3	1
influenza	1	1.4	1	0	0.0	0	1	1.3	1
pneumonia	1	1.4	1	0	0.0	0	1	1.3	1
urinary tract infection	1	1.4	1	0	0.0	0	1	1.3	1
vascular device infection	1	1.4	1	0	0.0	0	1	1.3	1
GASTROINTESTINAL DISORDERS	**5**	**6.9**	**7**	**1**	**12.5**	**1**	**6**	**7.5**	**8**
abdominal hernia	1	1.4	1	0	0.0	0	1	1.3	1
barrett's oesophagus	1	1.4	1	0	0.0	0	1	1.3	1
diarrhoea	1	1.4	1	0	0.0	0	1	1.3	1
gastritis	1	1.4	1	0	0.0	0	1	1.3	1
large intestine perforation	1	1.4	1	0	0.0	0	1	1.3	1
loose tooth	0	0.0	0	1	12.5	1	1	1.3	1
pancreatic disorder	1	1.4	1	0	0.0	0	1	1.3	1
umbilical hernia	1	1.4	1	0	0.0	0	1	1.3	1
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	**6**	**8.3**	**9**	**0**	**0.0**	**0**	**6**	**7.5**	**9**
haemophilic arthropathy	3	4.2	4	0	0.0	0	3	3.8	4
osteoarthritis	2	2.8	2	0	0.0	0	2	2.5	2
acquired claw toe	1	1.4	1	0	0.0	0	1	1.3	1
arthropathy	1	1.4	1	0	0.0	0	1	1.3	1
spinal stenosis	1	1.4	1	0	0.0	0	1	1.3	1

SYSTEM ORGAN CLASS preferred term	Hemophilia status								
	Severe (N=72)			Non-severe (N=8)			Total (N=80)		
	n	%	events	n	%	events	n	%	events
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	**4**	**5.6**	**6**	**1**	**12.5**	**1**	**5**	**6.3**	**7**
alcohol poisoning	1	1.4	1	0	0.0	0	1	1.3	1
fall	1	1.4	1	0	0.0	0	1	1.3	1
femoral neck fracture	1	1.4	1	0	0.0	0	1	1.3	1
incisional hernia	1	1.4	1	0	0.0	0	1	1.3	1
meniscus injury	0	0.0	0	1	12.5	1	1	1.3	1
periprosthetic fracture	1	1.4	1	0	0.0	0	1	1.3	1
post procedural myocardial infarction	1	1.4	1	0	0.0	0	1	1.3	1
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	**4**	**5.6**	**5**	**0**	**0.0**	**0**	**4**	**5.0**	**5**
general physical health deterioration	1	1.4	1	0	0.0	0	1	1.3	1
impaired healing	1	1.4	1	0	0.0	0	1	1.3	1
inflammation	1	1.4	1	0	0.0	0	1	1.3	1
malaise	1	1.4	1	0	0.0	0	1	1.3	1
multiple organ dysfunction syndrome	1	1.4	1	0	0.0	0	1	1.3	1
VASCULAR DISORDERS	**3**	**4.2**	**3**	**0**	**0.0**	**0**	**3**	**3.8**	**3**
hypertension	1	1.4	1	0	0.0	0	1	1.3	1
peripheral venous disease	1	1.4	1	0	0.0	0	1	1.3	1
thrombophlebitis	1	1.4	1	0	0.0	0	1	1.3	1
CARDIAC DISORDERS	**2**	**2.8**	**2**	**0**	**0.0**	**0**	**2**	**2.5**	**2**
atrial fibrillation	1	1.4	1	0	0.0	0	1	1.3	1
stress cardiomyopathy	1	1.4	1	0	0.0	0	1	1.3	1
NERVOUS SYSTEM DISORDERS	**2**	**2.8**	**2**	**0**	**0.0**	**0**	**2**	**2.5**	**2**
paraparesis	1	1.4	1	0	0.0	0	1	1.3	1
status epilepticus	1	1.4	1	0	0.0	0	1	1.3	1
INVESTIGATIONS	**1**	**1.4**	**1**	**0**	**0.0**	**0**	**1**	**1.3**	**1**
weight decreased	1	1.4	1	0	0.0	0	1	1.3	1
METABOLISM AND NUTRITION DISORDERS	**1**	**1.4**	**1**	**0**	**0.0**	**0**	**1**	**1.3**	**1**
propofol infusion syndrome	1	1.4	1	0	0.0	0	1	1.3	1
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	**1**	**1.4**	**1**	**0**	**0.0**	**0**	**1**	**1.3**	**1**
hepatocellular carcinoma	1	1.4	1	0	0.0	0	1	1.3	1
PSYCHIATRIC DISORDERS	**1**	**1.4**	**1**	**0**	**0.0**	**0**	**1**	**1.3**	**1**
depression	1	1.4	1	0	0.0	0	1	1.3	1
RENAL AND URINARY DISORDERS	**0**	**0.0**	**0**	**1**	**12.5**	**3**	**1**	**1.3**	**3**
haematuria	0	0.0	0	1	12.5	1	1	1.3	1
pollakiuria	0	0.0	0	1	12.5	1	1	1.3	1
urinary retention	0	0.0	0	1	12.5	1	1	1.3	1

Source: Appendix Table 14.5.1.3.1

MedDRA = Medical Dictionary for Regulatory Activities, N = number in analysis population, n = number of patients with event / in category, SAE = serious adverse event, SAF = Safety Analysis Set.

AEs were coded using MedDRA version 25.1.

12.6.3.1 Most Frequently Reported Serious Adverse Events

While Table 42 shows all SAEs, Table 43 shows only those preferred terms with an incidence of ≥2% in the “Severe” or “Non-severe” subgroup.

By SOC, most patients had SAEs related to the following: ”Infections and infestations” (7 [8.8%] patients, 9 events; 9 events in 7 [9.7%] patients in the severe and no events in the non-severe subgroup), ”Gastrointestinal disorders” (6 [7.5%] patients, 8 events; 7 events in 5 [6.9%] patients in the severe and 1 event in 1 [12.5%] patient in the non-severe subgroup) and ”Musculoskeletal and connective tissue disorders” (6 [7.5%] patients, 9 events; 9 events in 6 [8.3%] patients in the severe and no events in the non-severe subgroup).

By PT, the most commonly reported SAEs were ”Haemophilic arthropathy” (3 [3.8%] patients, 4 events; 4 events in 3 [4.2%] patients in the severe and no events in the non-severe subgroup), ”arthritis bacterial” (2 [2.5%] patients, 2 events; 2 events in 2 [2.8%] patients in the severe and no events in the non-severe subgroup) and “Osteoarthritis” (2 [2.5%] patients, 2 events; 2 events in 2 [2.8%] patients in the severe and no events in the non-severe subgroup). All other SAEs were single preferred terms in single patients.

Table 43 Serious adverse events by system organ class and preferred term in ≥2% of patients in the “Severe” or “Non-severe” subgroup at the preferred term level (SAF)

SYSTEM ORGAN CLASS preferred term	Hemophilia status								
	Severe (N=72)			Non-severe (N=8)			Total (N=80)		
	n	%	events	n	%	events	n	%	events
Patients with SAEs	**20**	**27.8**	**47**	**3**	**37.5**	**5**	**23**	**28.8**	**52**
INFECTIONS AND INFESTATIONS	**7**	**9.7**	**9**	**0**	**0.0**	**0**	**7**	**8.8**	**9**
arthritis bacterial	2	2.8	2	0	0.0	0	2	2.5	2
GASTROINTESTINAL DISORDERS	**5**	**6.9**	**7**	**1**	**12.5**	**1**	**6**	**7.5**	**8**
loose tooth	0	0.0	0	1	12.5	1	1	1.3	1
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	**6**	**8.3**	**9**	**0**	**0.0**	**0**	**6**	**7.5**	**9**
haemophilic arthropathy	3	4.2	4	0	0.0	0	3	3.8	4
osteoarthritis	2	2.8	2	0	0.0	0	2	2.5	2
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	**4**	**5.6**	**6**	**1**	**12.5**	**1**	**5**	**6.3**	**7**
meniscus injury	0	0.0	0	1	12.5	1	1	1.3	1
RENAL AND URINARY DISORDERS	**0**	**0.0**	**0**	**1**	**12.5**	**3**	**1**	**1.3**	**3**
haematuria	0	0.0	0	1	12.5	1	1	1.3	1
pollakiuria	0	0.0	0	1	12.5	1	1	1.3	1
urinary retention	0	0.0	0	1	12.5	1	1	1.3	1

Source: Appendix Table 14.5.1.3.1

MedDRA = Medical Dictionary for Regulatory Activities, N = number in analysis population, n = number of patients with event / in category, SAE = serious adverse event, SAF = Safety Analysis Set.

AEs were coded using MedDRA version 25.1.

12.6.3.2 Serious Adverse Events by Treatment Regimen

SAEs in SAF subgroups by treatment regimen are shown in Appendix Table 14.5.1.3.1.1.

In the subgroup “Prophylaxis <20 IU/kg 3 times per week” (N=14), 6 (42.9%) patients had 18 SAEs. All SAEs occurred in the “Severe” hemophilia subgroup and were single preferred terms in single patients. The only exception was the PT “Haemophilic arthropathy” that occurred twice in one patient.

In the subgroup “Prophylaxis ≥20 IU/kg 3 times per week” (N=26), 8 (30.8%) patients had 15 SAEs. All SAEs occurred in the “Severe” hemophilia subgroup and were single preferred terms in single patients. The only exception was again the PT “Haemophilic arthropathy” that occurred in two patients.

12.6.3.3 Serious Adverse Events in the Global PV Database

As described in Section 12.6.2.3, different approaches were taken in terms of the seriousness assessment in the clinical database and in the global PV database.

Table 44 provides a side-by-side comparison of SAEs from both databases, categorized by SOC and PT. In total, there were considerably fewer SAEs in the clinical database compared to the global PV database. One particular event stands out prominently in this comparison, namely MedDRA PT ”Haemarthrosis” of which none has been assessed as serious by any investigator.

In conclusion, it is essential to recognize that bleeding events, specifically spontaneous joint bleeding and hemarthrosis, are inherent to the underlying disease in patients with hemophilia. Given the known clinical features of hemophilia and the fact that patients primarily treated in this NIS belonged to the “Severe” subgroup, the differing assessments of seriousness for these bleeding events do not substantially impact the safety analysis of Haemoctin SDH.

Table 44 Comparative table of serious adverse events by system organ class and preferred term

SYSTEM ORGAN CLASS preferred term	Clinical Database Total (N=80)		Global PV Database Total (N=59*)	
	n	events	n	events
Patients with SAEs	**23**	**52**	**36**	**178**
INFECTIONS AND INFESTATIONS	**7**	**9**	**6**	**12**
arthritis bacterial	2	2	2	2
catheter site infection	-	-	1	1
cellulitis	1	1	1	1
diverticulitis	1	1	1	1
epididymitis	1	1	1	1
influenza	1	1	1	1
peritonitis	-	-	1	1
pilonidal disease	-	-	1	1
pneumonia	1	1	1	1
pneumonia bacterial	-	-	1	1
urinary tract infection	1	1	1	1
vascular device infection	1	1	-	-
GASTROINTESTINAL DISORDERS	**6**	**8**	**7**	**10**
abdominal hernia	1	1	1	1
barrett's oesophagus	1	1	1	1
diarrhoea	1	1	-	-
diverticulum intestinal	-	-	1	1
gastritis	1	1	1	1
gastrointestinal motility disorder	-	-	1	1
large intestine perforation	1	1	1	1
loose tooth	1	1	1	1
pancreatic disorder	1	1	1	1
umbilical hernia	1	1	2	2
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	**6**	**9**	**17**	**98**
haemarthrosis	-	-	12	84
haemophilic arthropathy	3	4	3	4
osteoarthritis	2	2	2	2
acquired claw toe	1	1	-	-
arthropathy	1	1	-	-
foot deformity	-	-	1	1
muscle haemorrhage	-	-	2	3
spinal stenosis	1	1	1	1
soft tissue haemorrhage	-	-	1	1
spondylolisthesis	-	-	1	1
synovitis	-	-	1	1

SYSTEM ORGAN CLASS preferred term	Clinical Database Total (N=80)		Global PV Database Total (N=59*)	
	n	events	n	events
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	**5**	**7**	**9**	**17**
alcohol poisoning	1	1	1	1
fall	1	1	3	3
femoral neck fracture	1	1	-	-
femur fracture	-	-	1	1
incisional hernia	1	1	1	1
meniscus injury	1	1	1	1
periprosthetic fracture	1	1	1	1
post procedural myocardial infarction	1	1	1	1
radius fracture	-	-	1	1
traumatic fracture	-	-	1	1
traumatic haemorrhage	-	-	2	6
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	**4**	**5**	**7**	**9**
Disease progression	-	-	2	3
general physical health deterioration	1	1	1	1
impaired healing	1	1	1	1
inflammation	1	1	1	1
malaise	1	1	1	1
mucosal haemorrhage	-	-	1	1
multiple organ dysfunction syndrome	1	1	1	1
VASCULAR DISORDERS	**3**	**3**	**5**	**5**
haematoma	-	-	1	1
haemorrhage	-	-	1	1
hypertension	1	1	1	1
peripheral venous disease	1	1	-	-
thrombophlebitis	1	1	1	1
vein disorder	-	-	1	1
CARDIAC DISORDERS	**2**	**2**	**3**	**3**
atrial fibrillation	1	1	2	2
stress cardiomyopathy	1	1	1	1
NERVOUS SYSTEM DISORDERS	**2**	**2**	**2**	**2**
paraparesis	1	1	1	1
status epilepticus	1	1	1	1
INVESTIGATIONS	**1**	**1**	**1**	**1**
weight decreased	1	1	1	1
METABOLISM AND NUTRITION DISORDERS	**1**	**1**	**1**	**1**
propofol infusion syndrome	1	1	1	1
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	**1**	**1**	**1**	**1**
hepatocellular carcinoma	1	1	1	1
PSYCHIATRIC DISORDERS	**1**	**1**	**1**	**1**
depression	1	1	1	1

SYSTEM ORGAN CLASS preferred term	Clinical Database Total (N=80)		Global PV Database Total (N=59*)	
	n	events	n	events
RENAL AND URINARY DISORDERS	**1**	**3**	**1**	**3**
haematuria	1	1	1	1
pollakiuria	1	1	1	1
urinary retention	1	1	1	1
SURGICAL AND MEDICAL PROCEDURES	**-**	**-**	**7**	**9**
colostomy closure	-	-	1	1
elective surgery	-	-	1	1
knee arthroplasty	-	-	2	2
umbilical hernia repair	-	-	1	1
hernia repair	-	-	1	1
skin lesion removal	-	-	1	1
arteriovenous fistula operation	-	-	1	1
tooth extraction	-	-	1	1
EYE DISORDERS	**-**	**-**	**1**	**1**
eye haemorrhage	-	-	1	1
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	**-**	**-**	**2**	**2**
epistaxis	-	-	1	1
respiratory failure	-	-	1	1
REPRODUCTIVE SYSTEM AND BREAST DISORDERS	**-**	**-**	**1**	**2**
prostatic haemorrhage	-	-	1	2
CONGENITAL, FAMILIAL AND GENETIC DISORDERS	**-**	**-**	**1**	**1**
factor II mutation	-	-	1	1

Source: Appendix Table 14.5.1.3.1, Appendix 2 in Section 17.2

MedDRA = Medical Dictionary for Regulatory Activities, N = number in analysis population, n = number of patients with event / in category, SAE = serious adverse event, SAF = Safety Analysis Set.

* In the global PV database, only patients experiencing adverse events are counted. Patients without adverse events are not captured in this dataset

AEs of the clinical database were coded using MedDRA version 25.1. AEs of the global PV database were coded using MedDRA version 26.0.

12.6.4 Adverse Events of Special Interest

According to the SAP (final version 1.0, 25-Jan-2023; Section 5.3.7), AESIs included bleeding episodes in general and of high relevance (all major bleeds, e.g., gastrointestinal bleeds, joint bleeds or intracranial hemorrhage, bleeds with unexpected course or severity in context of the underlying situation). In addition, AEs with bleeding and AEs resulting in bleeding were also captured as AESIs. All AEs that were categorized as type “Bleeding” by the investigator in the eCRF were used for the corresponding analysis.

AESIs are presented by patient in Appendix Listing 16.2.23.3 together with the clinically meaningful AEs.

12.6.4.1 AESIs in the Total SAF

AESIs are tabulated by SOC and PT in Table 14.5.1.6.1 and in Table 45.

In the total SAF, 48 (60.0%) patients had 756 AESIs. The most common AESIs (in ≥10% of patients) were “Haemarthrosis” (in 18 [22.5%] patients, 179 events; SOC “Musculoskeletal and connective tissue disorders”), “Spontaneous haemorrhage” (in 14 [17.5%] patients, 217 events; SOC “Blood and lymphatic system disorders”), “Haemorrhage” (in 13 [16.3%] patients, 282 events; SOC “Vascular disorders”) and “Traumatic haemorrhage” (in 9 [11.3%] patients, 15 events; SOC “Injury, poisoning and procedural complication”).

Among the 179 events of the most common preferred term “Haemarthrosis”, 114 events in 15 (18.8%) patients were of mild severity, 35 events in 8 (10.0%) patients were of moderate severity and 1 event in 1 (1.3%) patient was severe (severity not available for 29 further events).

Table 45 Adverse events of special interest by system organ class and preferred term (SAF)

SYSTEM ORGAN CLASS preferred term	Hemophilia status								
	Severe (N=72)			Non-severe (N=8)			Total (N=80)		
	n	%	events	n	%	events	n	%	events
Patients with AESIs (Bleedings)	**44**	**61.1**	**747**	**4**	**50.0**	**9**	**48**	**60.0**	**756**
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	**17**	**23.6**	**28**	**1**	**12.5**	**5**	**18**	**22.5**	**33**
traumatic haemorrhage	9	12.5	15	0	0.0	0	9	11.3	15
fall	3	4.2	3	0	0.0	0	3	3.8	3
joint injury	2	2.8	2	1	12.5	1	3	3.8	3
contusion	2	2.8	2	0	0.0	0	2	2.5	2
limb injury	1	1.4	2	1	12.5	4	2	2.5	6
wound	2	2.8	2	0	0.0	0	2	2.5	2
bite	1	1.4	1	0	0.0	0	1	1.3	1
head injury	1	1.4	1	0	0.0	0	1	1.3	1
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	**16**	**22.2**	**187**	**2**	**25.0**	**2**	**18**	**22.5**	**189**
haemarthrosis	16	22.2	177	2	25.0	2	18	22.5	179
muscle haemorrhage	5	6.9	6	0	0.0	0	5	6.3	6
arthralgia	2	2.8	2	0	0.0	0	2	2.5	2
joint effusion	1	1.4	1	0	0.0	0	1	1.3	1
soft tissue swelling	1	1.4	1	0	0.0	0	1	1.3	1
VASCULAR DISORDERS	**16**	**22.2**	**289**	**1**	**12.5**	**1**	**17**	**21.3**	**290**
haemorrhage	12	16.7	281	1	12.5	1	13	16.3	282
haematoma	5	6.9	8	0	0.0	0	5	6.3	8

SYSTEM ORGAN CLASS preferred term	Hemophilia status								
	Severe (N=72)			Non-severe (N=8)			Total (N=80)		
	n	%	events	n	%	events	n	%	events
BLOOD AND LYMPHATIC SYSTEM DISORDERS	**14**	**19.4**	**217**	**0**	**0.0**	**0**	**14**	**17.5**	**217**
spontaneous haemorrhage	14	19.4	217	0	0.0	0	14	17.5	217
GASTROINTESTINAL DISORDERS	**4**	**5.6**	**5**	**0**	**0.0**	**0**	**4**	**5.0**	**5**
gingival bleeding	2	2.8	2	0	0.0	0	2	2.5	2
haematochezia	1	1.4	1	0	0.0	0	1	1.3	1
intra-abdominal haematoma	1	1.4	1	0	0.0	0	1	1.3	1
mouth haemorrhage	1	1.4	1	0	0.0	0	1	1.3	1
RENAL AND URINARY DISORDERS	**2**	**2.8**	**2**	**1**	**12.5**	**1**	**3**	**3.8**	**3**
haematuria	2	2.8	2	1	12.5	1	3	3.8	3
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	**3**	**4.2**	**6**	**0**	**0.0**	**0**	**3**	**3.8**	**6**
epistaxis	3	4.2	6	0	0.0	0	3	3.8	6
EYE DISORDERS	**2**	**2.8**	**5**	**0**	**0.0**	**0**	**2**	**2.5**	**5**
conjunctival haemorrhage	1	1.4	4	0	0.0	0	1	1.3	4
eye haemorrhage	1	1.4	1	0	0.0	0	1	1.3	1
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	**2**	**2.8**	**5**	**0**	**0.0**	**0**	**2**	**2.5**	**5**
nail bed bleeding	1	1.4	1	0	0.0	0	1	1.3	1
skin haemorrhage	1	1.4	4	0	0.0	0	1	1.3	4
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	**1**	**1.4**	**1**	**0**	**0.0**	**0**	**1**	**1.3**	**1**
mucosal haemorrhage	1	1.4	1	0	0.0	0	1	1.3	1
REPRODUCTIVE SYSTEM AND BREAST DISORDERS	**1**	**1.4**	**1**	**0**	**0.0**	**0**	**1**	**1.3**	**1**
benign prostatic hyperplasia	1	1.4	1	0	0.0	0	1	1.3	1
SURGICAL AND MEDICAL PROCEDURES	**1**	**1.4**	**1**	**0**	**0.0**	**0**	**1**	**1.3**	**1**
wisdom teeth removal	1	1.4	1	0	0.0	0	1	1.3	1

Source: Appendix Table 14.5.1.6.1

AE = adverse event, AESI = adverse events of special interest, MedDRA = Medical Dictionary for Regulatory Activities, N = number in analysis population, n = number of patients with event / in category, SAF = Safety Analysis Set.

AEs were coded using MedDRA version 25.1.

12.6.4.2 AESIs in SAF Subgroups by Treatment Regimen

AESIs in SAF subgroups by treatment regimen are shown in Appendix Table 14.5.1.6.1.1 and Table 46 to Table 48.

AESIs in the SAF subgroup “Prophylaxis” are shown in Table 46. The patients in this subgroup (N=75) are identical to the patients in the SAF apart from 5 missing patients. The results are therefore similar between the “Prophylaxis” subgroup and the SAF (Table 46, Table 45).

Table 46 Adverse events of special interest by system organ class and preferred term in the subgroup "Prophylaxis" (SAF)

SYSTEM ORGAN CLASS preferred term	Hemophilia status Severe (N=71)			Non-severe (N=4)			Total (N=75)		
	n	%	events	n	%	events	n	%	events
Patients with AESIs (Bleedings)	**43**	**60.6**	**731**	**2**	**50.0**	**2**	**45**	**60.0**	**733**
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	**17**	**23.9**	**28**	**0**	**0.0**	**0**	**17**	**22.7**	**28**
traumatic haemorrhage	9	12.7	15	0	0.0	0	9	12.0	15
fall	3	4.2	3	0	0.0	0	3	4.0	3
contusion	2	2.8	2	0	0.0	0	2	2.7	2
joint injury	2	2.8	2	0	0.0	0	2	2.7	2
wound	2	2.8	2	0	0.0	0	2	2.7	2
bite	1	1.4	1	0	0.0	0	1	1.3	1
head injury	1	1.4	1	0	0.0	0	1	1.3	1
limb injury	1	1.4	2	0	0.0	0	1	1.3	2
VASCULAR DISORDERS	**16**	**22.5**	**289**	**1**	**25.0**	**1**	**17**	**22.7**	**290**
haemorrhage	12	16.9	281	1	25.0	1	13	17.3	282
haematoma	5	7.0	8	0	0.0	0	5	6.7	8
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	**15**	**21.1**	**172**	**0**	**0.0**	**0**	**15**	**20.0**	**172**
haemarthrosis	15	21.1	162	0	0.0	0	15	20.0	162
muscle haemorrhage	5	7.0	6	0	0.0	0	5	6.7	6
arthralgia	2	2.8	2	0	0.0	0	2	2.7	2
joint effusion	1	1.4	1	0	0.0	0	1	1.3	1
soft tissue swelling	1	1.4	1	0	0.0	0	1	1.3	1
BLOOD AND LYMPHATIC SYSTEM DISORDERS	**13**	**18.3**	**216**	**0**	**0.0**	**0**	**13**	**17.3**	**216**
spontaneous haemorrhage	13	18.3	216	0	0.0	0	13	17.3	216
GASTROINTESTINAL DISORDERS	**4**	**5.6**	**5**	**0**	**0.0**	**0**	**4**	**5.3**	**5**
gingival bleeding	2	2.8	2	0	0.0	0	2	2.7	2
haematochezia	1	1.4	1	0	0.0	0	1	1.3	1
intra-abdominal haematoma	1	1.4	1	0	0.0	0	1	1.3	1
mouth haemorrhage	1	1.4	1	0	0.0	0	1	1.3	1
RENAL AND URINARY DISORDERS	**2**	**2.8**	**2**	**1**	**25.0**	**1**	**3**	**4.0**	**3**
haematuria	2	2.8	2	1	25.0	1	3	4.0	3
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	**3**	**4.2**	**6**	**0**	**0.0**	**0**	**3**	**4.0**	**6**
epistaxis	3	4.2	6	0	0.0	0	3	4.0	6
EYE DISORDERS	**2**	**2.8**	**5**	**0**	**0.0**	**0**	**2**	**2.7**	**5**
conjunctival haemorrhage	1	1.4	4	0	0.0	0	1	1.3	4
eye haemorrhage	1	1.4	1	0	0.0	0	1	1.3	1
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	**2**	**2.8**	**5**	**0**	**0.0**	**0**	**2**	**2.7**	**5**
nail bed bleeding	1	1.4	1	0	0.0	0	1	1.3	1
skin haemorrhage	1	1.4	4	0	0.0	0	1	1.3	4

SYSTEM ORGAN CLASS preferred term	Hemophilia status								
	Severe (N=71)			Non-severe (N=4)			Total (N=75)		
	n	%	events	n	%	events	n	%	events
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	**1**	**1.4**	**1**	**0**	**0.0**	**0**	**1**	**1.3**	**1**
mucosal haemorrhage	1	1.4	1	0	0.0	0	1	1.3	1
REPRODUCTIVE SYSTEM AND BREAST DISORDERS	**1**	**1.4**	**1**	**0**	**0.0**	**0**	**1**	**1.3**	**1**
benign prostatic hyperplasia	1	1.4	1	0	0.0	0	1	1.3	1
SURGICAL AND MEDICAL PROCEDURES	**1**	**1.4**	**1**	**0**	**0.0**	**0**	**1**	**1.3**	**1**
wisdom teeth removal	1	1.4	1	0	0.0	0	1	1.3	1

Source: Appendix Table 14.5.1.6.1.1

AE = adverse event, AESI = adverse events of special interest, MedDRA = Medical Dictionary for Regulatory Activities, N = number in analysis population, n = number of patients with event / in category, SAF = Safety Analysis Set.

AEs were coded using MedDRA version 25.1.

AESIs in the SAF subgroup “Prophylaxis <20 IU/kg 3 times per week” are shown in Table 47. The most common AESIs in this subgroup were “Haemarthrosis” (in 8 [57.1%] patients, 130 events; SOC “Musculoskeletal and connective tissue disorders”; 88 mild, 32 moderate and 1 severe event; severity not available for 9 events) and “Haemorrhage” (in 8 [57.1%] patients, 170 events; SOC “Vascular disorders”; 148 mild and 9 moderate events, severity of 13 events not available) (Table 47; Appendix Table 14.5.1.6.1.1).

Table 47 Adverse events of special interest by system organ class and preferred term in the subgroup "Prophylaxis <20 IU/kg 3 times per week" (SAF)

SYSTEM ORGAN CLASS preferred term	Hemophilia status								
	Severe (N=12)			Non-severe (N=2)			Total (N=14)		
	n	%	events	n	%	events	n	%	events
Patients with AESIs - Bleedings	**11**	**91.7%**	**327**	**1**	**50.0**	**1**	**12**	**85.7%**	**328**
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	**8**	**66.7**	**136**	**0**	**0.0**	**0**	**8**	**57.1**	**136**
haemarthrosis	8	66.7	130	0	0.0	0	8	57.1	130
muscle haemorrhage	5	41.7	6	0	0.0	0	5	35.7	6
VASCULAR DISORDERS	**7**	**58.3**	**170**	**1**	**50.0**	**1**	**8**	**57.1**	**171**
haemorrhage	7	58.3	169	1	50.0	1	8	57.1	170
haematoma	1	8.3	1	0	0.0	0	1	7.1	1
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	**5**	**41.7**	**8**	**0**	**0.0**	**0**	**5**	**35.7**	**8**
traumatic haemorrhage	2	16.7	5	0	0.0	0	2	14.3	5
bite	1	8.3	1	0	0.0	0	1	7.1	1
contusion	1	8.3	1	0	0.0	0	1	7.1	1
fall	1	8.3	1	0	0.0	0	1	7.1	1
GASTROINTESTINAL DISORDERS	**2**	**16.7**	**3**	**0**	**0.0**	**0**	**2**	**14.3**	**3**
haematochezia	1	8.3	1	0	0.0	0	1	7.1	1
intra-abdominal haematoma	1	8.3	1	0	0.0	0	1	7.1	1
mouth haemorrhage	1	8.3	1	0	0.0	0	1	7.1	1
RENAL AND URINARY DISORDERS	**2**	**16.7**	**2**	**0**	**0.0**	**0**	**2**	**14.3**	**2**
haematuria	2	16.7	2	0	0.0	0	2	14.3	2
BLOOD AND LYMPHATIC SYSTEM DISORDERS	**1**	**8.3**	**1**	**0**	**0.0**	**0**	**1**	**7.1**	**1**
spontaneous haemorrhage	1	8.3	1	0	0.0	0	1	7.1	1
EYE DISORDERS	**1**	**8.3**	**1**	**0**	**0.0**	**0**	**1**	**7.1**	**1**
eye haemorrhage	1	8.3	1	0	0.0	0	1	7.1	1
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	**1**	**8.3**	**1**	**0**	**0.0**	**0**	**1**	**7.1**	**1**
epistaxis	1	8.3	1	0	0.0	0	1	7.1	1
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	**1**	**8.3**	**4**	**0**	**0.0**	**0**	**1**	**7.1**	**4**
skin haemorrhage	1	8.3	4	0	0.0	0	1	7.1	4
SURGICAL AND MEDICAL PROCEDURES	**1**	**8.3**	**1**	**0**	**0.0**	**0**	**1**	**7.1**	**1**
wisdom teeth removal	1	8.3	1	0	0.0	0	1	7.1	1

Source: Appendix Table 14.5.1.6.1.1

AE = adverse event, AESI = adverse events of special interest, MedDRA = Medical Dictionary for Regulatory Activities, N = number in analysis population, n = number of patients with event / in category, SAF = Safety Analysis Set.

AEs were coded using MedDRA version 25.1.

AESIs in the SAF subgroup "Prophylaxis ≥20 IU/kg 3 times per week" are shown in Table 48. The most common AESIs in this subgroup were "Traumatic haemorrhage" (in 5 [19.2%] patients, 6 events; SOC "Injury, poisoning and procedural complications"; 4 mild and 2 moderate events), "Spontaneous haemorrhage" (in 4 [15.4%] patients, 16 events;

SOC “Blood and lymphatic system disorders”; 10 mild and 6 moderate events) and “Haemarthrosis” (in 4 [15.4%] patients, 23 events; SOC “Musculoskeletal and connective tissue disorders”; 1 mild and 2 moderate events, severity of 20 events not available) (Table 48; Appendix Table 14.5.1.6.1.1).

Table 48 Adverse events of special interest by system organ class and preferred term in the subgroup “Prophylaxis ≥20 IU/kg 3 times per week” (SAF)

SYSTEM ORGAN CLASS preferred term	Hemophilia status								
	Severe (N=26)			Non-severe (N=0)			Total (N=26)		
	n	%	events	n	%	events	n	%	events
Patients with AESIs - Bleedings	**15**	**57.7**	**68**	**0**	**0.0**	**0**	**15**	**57.7**	**68**
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	**7**	**26.9**	**13**	**0**	**0.0**	**0**	**7**	**26.9**	**13**
traumatic haemorrhage	5	19.2	6	0	0.0	0	5	19.2	6
wound	2	7.7	2	0	0.0	0	2	7.7	2
fall	1	3.8	1	0	0.0	0	1	3.8	1
head injury	1	3.8	1	0	0.0	0	1	3.8	1
joint injury	1	3.8	1	0	0.0	0	1	3.8	1
limb injury	1	3.8	2	0	0.0	0	1	3.8	2
BLOOD AND LYMPHATIC SYSTEM DISORDERS	**4**	**15.4**	**16**	**0**	**0.0**	**0**	**4**	**15.4**	**16**
spontaneous haemorrhage	4	15.4	16	0	0.0	0	4	15.4	16
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	**4**	**15.4**	**26**	**0**	**0.0**	**0**	**4**	**15.4**	**26**
haemarthrosis	4	15.4	23	0	0.0	0	4	15.4	23
arthralgia	1	3.8	1	0	0.0	0	1	3.8	1
joint effusion	1	3.8	1	0	0.0	0	1	3.8	1
soft tissue swelling	1	3.8	1	0	0.0	0	1	3.8	1
GASTROINTESTINAL DISORDERS	**2**	**7.7**	**2**	**0**	**0.0**	**0**	**2**	**7.7**	**2**
gingival bleeding	2	7.7	2	0	0.0	0	2	7.7	2
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	**2**	**7.7**	**5**	**0**	**0.0**	**0**	**2**	**7.7**	**5**
epistaxis	2	7.7	5	0	0.0	0	2	7.7	5
VASCULAR DISORDERS	**2**	**7.7**	**3**	**0**	**0.0**	**0**	**2**	**7.7**	**3**
haematoma	2	7.7	3	0	0.0	0	2	7.7	3
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	**1**	**3.8**	**1**	**0**	**0.0**	**0**	**1**	**3.8**	**1**
mucosal haemorrhage	1	3.8	1	0	0.0	0	1	3.8	1
REPRODUCTIVE SYSTEM AND BREAST DISORDERS	**1**	**3.8**	**1**	**0**	**0.0**	**0**	**1**	**3.8**	**1**
benign prostatic hyperplasia	1	3.8	1	0	0.0	0	1	3.8	1
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	**1**	**3.8**	**1**	**0**	**0.0**	**0**	**1**	**3.8**	**1**
nail bed bleeding	1	3.8	1	0	0.0	0	1	3.8	1

Source: Appendix Table 14.5.1.6.1.1

AE = adverse event, AESI = adverse events of special interest, MedDRA = Medical Dictionary for Regulatory Activities, N = number in analysis population, n = number of patients with event / in category, SAF = Safety Analysis Set.

AEs were coded using MedDRA version 25.1.

The comparison of the prophylaxis regimens, specifically "<20 IU/kg 3 times per week" and “≥20 IU/kg 3 times per week”, lacks strong conclusiveness due to a relatively low number of patients in both groups. However, occurrences of AESIs, primarily associated with the underlying disease, were notably higher in patients receiving prophylaxis with "<20 IU/kg 3 times per week" (328 AESIs in 12 [85.7%] of 14 patients; Table 47) compared to those on the regimen of “≥20 IU/kg 3 times per week” (68 AESIs in 15 [57.7%] of 26 patients; Table 48).

Considering the SmPC recommendation for Haemoctin SDH prophylaxis of “≥20 IU/kg 3 times per week”, it was expected that a higher number of bleeding events would occur in patients on the prophylaxis regimen of “<20 IU/kg 3 times per week”.

12.6.4.3 AESIs in the Global PV Database

As detailed in Section 12.6.2.3, there are coding differences primarily centered around bleeding events when comparing entries from the clinical database and the global PV database.

Table 49 offers a side-by-side comparison of AESIs from both databases, categorized by SOC and PT.

The clinical database lists significantly more MedDRA PTs such as “Haemorrhages” (282 vs. 42 events) and “Spontaneous haemorrhages” (217 vs. 49 events) in comparison to the global PV database. Conversely, the latter reports notably more occurrences of “Haemarthrosis” (568 vs. 180 events).

Apart from these, no other relevant differences are evident. Understanding that bleeding events are inherent to the disease itself, the variations in terminology do not compromise the overall safety evaluation of the drug in this patient population.

Table 49 Comparative table of AESIs by system organ class and preferred term

SYSTEM ORGAN CLASS preferred term	Clinical Database (N=80)		Global PV Database (N=59*)	
	n	events	n	events
Patients with AESIs (Bleedings)	**48**	**756**	**51**	**819**
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	**18**	**33**	**20**	**69**
traumatic haemorrhage	9	15	15	31
fall	3	3	6	21
joint injury	3	3	1	1
contusion	2	2	4	5
limb injury	2	6	2	2
wound	2	2	2	2
bite	1	1	1	1
head injury	1	1	-	-
traumatic haematoma	-	-	3	4
procedural haemorrhage	-	-	1	1
post procedural haemorrhage	-	-	1	1
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	**18**	**189**	**36**	**592**
haemarthrosis	18	179	32	568
soft tissue haemorrhage	-	-	1	1
muscle haemorrhage	5	6	7	8
arthralgia	2	2	9	12
joint effusion	1	1	1	1
soft tissue swelling	1	1	-	-
VASCULAR DISORDERS	**17**	**290**	**15**	**48**
haemorrhage	13	282	11	42
haematoma	5	8	4	6
BLOOD AND LYMPHATIC SYSTEM DISORDERS	**14**	**217**	**9**	**49**
spontaneous haemorrhage	14	217	9	49
GASTROINTESTINAL DISORDERS	**4**	**5**	**6**	**10**
gingival bleeding	2	2	2	2
haematochezia	1	1	1	1
intra-abdominal haematoma	1	1	1	1
mouth haemorrhage	1	1	2	2
haemorrhoidal haemorrhage	-	-	1	2
intra-abdominal haemorrhage	-	-	1	1
rectal haemorrhage	-	-	1	1
RENAL AND URINARY DISORDERS	**3**	**3**	**4**	**7**
haematuria	3	3	4	7
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	**3**	**6**	**6**	**25**
epistaxis	3	6	6	25
EYE DISORDERS	**2**	**5**	**3**	**11**
conjunctival haemorrhage	1	4	1	4
eye haemorrhage	1	1	2	7
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	**2**	**5**	**2**	**4**
nail bed bleeding	1	1	1	1
skin haemorrhage	1	4	1	3

SYSTEM ORGAN CLASS preferred term	Clinical Database (N=80) n	 events	Global PV Database (N=59*) n	 events
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	**1**	**1**	**1**	**1**
mucosal haemorrhage	1	1	1	1
REPRODUCTIVE SYSTEM AND BREAST DISORDERS	**1**	**1**	**1**	**2**
benign prostatic hyperplasia	1	1	-	
prostatic haemorrhage			1	2
SURGICAL AND MEDICAL PROCEDURES	**1**	**1**	**1**	**1**
wisdom teeth removal	1	1	1	1

Source: Appendix Table 14.5.1.6.1, Appendix 2 in Section 17.2

AE = adverse event, AESI = adverse events of special interest, MedDRA = Medical Dictionary for Regulatory Activities, N = number in analysis population, n = number of patients with event / in category, SAF = Safety Analysis Set.

* In the global PV database, only patients experiencing AEs are counted. Patients without AEs are not captured in this dataset.

AEs of the clinical database were coded using MedDRA version 25.1. AEs of the global PV database were coded using MedDRA version 26.0.

12.6.4.4 Serious AESIs in the Total SAF

Serious AESIs are tabulated by SOC and PT in Table 14.5.1.8.1. In addition, serious AESIs are presented by patient in Appendix Listing 16.2.23.4 together with the clinically meaningful AEs.

In the SAF (non-severe hemophilia status), 1 AESI was serious as assessed by the investigator, i.e., “Haematuria” (1 [1.3%] patient, 1 event; SOC “Renal and urinary disorders”).

12.6.4.5 Serious AESIs in SAF Subgroups by Treatment Regimen

Serious AESIs in SAF subgroups by treatment regimen are shown in Appendix Table 14.5.1.8.1.1.

The patient who experienced the serious AESI “Haematuria” belonged to the subgroup “Prophylaxis”.

12.6.5 Other Clinically Meaningful Adverse Events

The following 4 specific AE categories (defined by the following search strings) were considered clinically meaningful:

- Thromboembolic events (AEs identified by Standardized MedDRA Query [SMQ] narrow: Embolic and thrombotic events)
- Hypersensitivity / Anaphylactic reactions (AEs identified by SMQs broad: Hypersensitivity; Anaphylactic reaction)
- Development of anti-FVIII inhibitors (AEs identified by MedDRA preferred terms: Anti-FVIII antibody positive, Anti-factor FVIII antibody test, and FVIII inhibition)
- Transmission of infective agents (AEs identified by MedDRA preferred terms: Transmission of infectious agent via product, Suspected transmission of infectious agent via product)

These AEs are shown in Appendix Table 14.5.1.6.1 through Table 14.5.1.8.1.1 together with the AESIs and are presented separately in Table 50.

Table 50 Other clinically meaningful AEs by system organ class and preferred term (SAF)

SYSTEM ORGAN CLASS preferred term	Hemophilia status Severe (N=72) n	%	events	Non-severe (N=8) n	%	events	Total (N=80) n	%	events
Thromboembolic events[1]									
Patients with thromboembolic events	**4**	**5.6**	**4**	**0**	**0.0**	**0**	**4**	**5.0**	**4**
CARDIAC DISORDERS	**1**	**1.4**	**1**	**0**	**0.0**	**0**	**1**	**1.3**	**1**
stress cardiomyopathy	1	1.4	1	0	0.0	0	1	1.3	1
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	**1**	**1.4**	**1**	**0**	**0.0**	**0**	**1**	**1.3**	**1**
post procedural myocardial infarction	1	1.4	1	0	0.0	0	1	1.3	1
NERVOUS SYSTEM DISORDERS	**1**	**1.4**	**1**	**0**	**0.0**	**0**	**1**	**1.3**	**1**
paraparesis	1	1.4	1	0	0.0	0	1	1.3	1
VASCULAR DISORDERS	**1**	**1.4**	**1**	**0**	**0.0**	**0**	**1**	**1.3**	**1**
thrombophlebitis	1	1.4	1	0	0.0	0	1	1.3	1
Hypersensitivity / Anaphylactic reactions[2]									
Patients with hypersensitivity / anaphylactic reactions	**8**	**11.1**	**10**	**0**	**0.0**	**0**	**8**	**10.0**	**10**
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	**4**	**5.6**	**6**	**0**	**0.0**	**0**	**4**	**5.0**	**6**
localised oedema	2	2.8	4	0	0.0	0	2	2.5	4
chest discomfort	1	1.4	1	0	0.0	0	1	1.3	1
swelling	1	1.4	1	0	0.0	0	1	1.3	1
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	**2**	**2.8**	**2**	**0**	**0.0**	**0**	**2**	**2.5**	**2**
cough	2	2.8	2	0	0.0	0	2	2.5	2
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	**2**	**2.8**	**2**	**0**	**0.0**	**0**	**2**	**2.5**	**2**
dermatitis	1	1.4	1	0	0.0	0	1	1.3	1
urticaria	1	1.4	1	0	0.0	0	1	1.3	1
Development of anti-FVIII inhibitors[3]									
Patients with development of anti-FVIII inhibitors	**0**	**0.0**	**0**	**0**	**0.0**	**0**	**0**	**0.0**	**0**
Transmission of infective agents[4]									
Patients with transmission of infective agents	**0**	**0.0**	**0**	**0**	**0.0**	**0**	**0**	**0.0**	**0**

Source: Appendix Table 14.5.1.6.1

AE = adverse event, FVIII = factor VIII, MedDRA = Medical Dictionary for Regulatory Activities, N = number in analysis population, n = number of patients with event / in category, SAF = Safety Analysis Set, SMQ = Standardized MedDRA Query.

Definition of AE categories:

[1] Thromboembolic events: AEs identified by MedDRA SMQs narrow: Embolic and thrombotic events.

[2] Hypersensitivity / Anaphylactic reactions: AEs identified by MedDRA SMQs broad: Hypersensitivity / Anaphylactic reaction.

[3] Development of anti-FVIII inhibitors: AEs identified by MedDRA preferred terms: Anti-FVIII antibody positive, anti-factor FVIII antibody test, and FVIII inhibition.

[4] Transmission of infective agents: AEs identified by MedDRA preferred terms: Transmission of infectious agent via product, Suspected transmission of infectious agent via product.

AEs were coded using MedDRA version 25.1.

12.6.5.1 Thromboembolic Events

In the total SAF, 4 (5.0%) patients experienced 4 AEs of the category “Thromboembolic events”. All 4 events were reported as serious. These were the preferred terms “Stress cardiomyopathy” (SOC “Cardiac disorders”; severe), “Post procedural myocardial infarction” (SOC “Injury, poisoning and procedural complications”; severe), “Paraparesis” (SOC “Nervous system disorders”; moderate) and “Thrombophlebitis” (SOC “Vascular disorders”; moderate) in 1 (1.3%) patient each (Table 50, Appendix Table 14.5.1.6.1).

None of the events of this category was assessed by the investigators as related to the administration of Haemoctin SDH.

12.6.5.2 Hypersensitivity / Anaphylactic Reactions

In the total SAF, 8 (10.0%) patients experienced 10 AEs of the category “Hypersensitivity / Anaphylactic reactions”. All 10 events were reported as non-serious. The preferred terms “Localised oedema” (SOC “General disorders and administration site conditions”; all mild) and “Cough” (SOC “Respiratory, thoracic and mediastinal disorders”; both moderate) occurred in 2 (2.5%) patients each. The preferred terms “Chest discomfort” and “Swelling” (both SOC “General disorders and administration site conditions”; the former AE was moderate, the latter mild) as well as “Dermatitis” and “Urticaria” (both SOC “Skin and subcutaneous tissue disorders”; the former AE was moderate, the latter mild) occurred in 1 (1.3%) patient each (Table 50, Appendix Table 14.5.1.6.1).

None of the events of this category was assessed by the investigators as related to the administration of Haemoctin SDH.

12.6.5.3 Development of Anti-FVIII Inhibitors

Overall, no AEs of the category “Development of anti-FVIII inhibitors” were reported in the study (Table 50, Appendix Table 14.5.1.6.1).

12.6.5.4 Transmission of Infective Agents

Overall, no AEs of the category “Transmission of infective agents” were reported in the study (Table 50, Appendix Table 14.5.1.6.1).

12.6.6 Adverse Events Resulting in Death

In the SAF, 4 AEs in 1 (1.3%) patient resulted in death. These fatal AEs were “Stress cardiomyopathy” (SOC “Cardiac disorders”), “Multiple organ dysfunction syndrome” (SOC “General disorders and administration site conditions”), “Propofol infusion syndrome” (SOC

"Metabolism and nutrition disorders") and "Status epilepticus" (SOC "Nervous system disorders") (Table 51). The investigator assessed all these 4 fatal AEs to be not related to Haemoctin SDH.

The patient who died from the fatal AEs was included in the SAF and the PSAF, but not in the FAS because no bleeding score assessments were available. The patient belonged to the following subgroups: hemophilia status, "Severe"; treatment regimen, "Prophylaxis" and "Prophylaxis ≥20 IU/kg 3 times per week"; previous treatment, "previously treated patient" (Appendix Listings 16.2.2 and 16.2.23.5). AEs resulting in death are shown in subgroups by treatment regimen in Appendix Table 14.5.1.10.1.1 and are presented by patient in Appendix Listing 16.2.23.5.

Table 51 Adverse events resulting in death (SAF)

SYSTEM ORGAN CLASS preferred term	Hemophilia status								
	Severe (N=72)			Non-severe (N=8)			Total (N=80)		
	n	%	events	n	%	events	n	%	events
Patients with AEs resulting in death	**1**	**1.4**	**4**	**0**	**0.0**	**0**	**1**	**1.3**	**4**
CARDIAC DISORDERS	**1**	**1.4**	**1**	**0**	**0.0**	**0**	**1**	**1.3**	**1**
stress cardiomyopathy	1	1.4	1	0	0.0	0	1	1.3	1
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	**1**	**1.4**	**1**	**0**	**0.0**	**0**	**1**	**1.3**	**1**
multiple organ dysfunction syndrome	1	1.4	1	0	0.0	0	1	1.3	1
METABOLISM AND NUTRITION DISORDERS	**1**	**1.4**	**1**	**0**	**0.0**	**0**	**1**	**1.3**	**1**
propofol infusion syndrome	1	1.4	1	0	0.0	0	1	1.3	1
NERVOUS SYSTEM DISORDERS	**1**	**1.4**	**1**	**0**	**0.0**	**0**	**1**	**1.3**	**1**
status epilepticus	1	1.4	1	0	0.0	0	1	1.3	1

Source: Appendix Table 14.5.1.10.1.

AE = adverse event, N = number in analysis population, n = number of patients with event / in category, SAF = Safety Analysis Set.

12.6.7 Adverse Events Leading to Haemoctin SDH Discontinuation

In the SAF, 4 AE led to Haemoctin SDH discontinuation. The preferred terms were "General physical health deterioration" and "Multiple organ dysfunction syndrome" (both SOC "General disorders and administration site conditions"; both severe), "Haemophilic arthropathy" (SOC "Musculoskeletal and connective tissue disorders"; mild) and "haematuria" (SOC "Renal and urinary disorders"; severe) in 1 (1.3%) patient each (Table 52; Appendix Table 14.5.1.11.1). AEs leading to Haemoctin SDH discontinuation are presented by patient in Appendix Listing 16.2.23.6.

AEs leading to Haemoctin SDH discontinuation are shown in subgroups by treatment regimen in Appendix Table 14.5.1.11.1.1.

Table 52 Adverse events leading to Haemoctin SDH discontinuation (SAF)

SYSTEM ORGAN CLASS preferred term	Hemophilia status								
	Severe (N=72)			Non-severe (N=8)			Total (N=80)		
	n	%	events	n	%	events	n	%	events
Patients with AEs leading to Haemoctin SDH discontinuation	**2**	**2.8**	**2**	**2**	**25.0**	**2**	**4**	**5.0**	**4**
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	**1**	**1.4**	**1**	**1**	**12.5**	**1**	**2**	**2.5**	**2**
general physical health deterioration	0	0.0	0	1	12.5	1	1	1.3	1
multiple organ dysfunction syndrome	1	1.4	1	0	0.0	0	1	1.3	1
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	**1**	**1.4**	**1**	**0**	**0.0**	**0**	**1**	**1.3**	**1**
haemophilic arthropathy	1	1.4	1	0	0.0	0	1	1.3	1
RENAL AND URINARY DISORDERS	**0**	**0.0**	**0**	**1**	**12.5**	**1**	**1**	**1.3**	**1**
haematuria	0	0.0	0	1	12.5	1	1	1.3	1

Source: Appendix Table 14.5.1.11.1.

AE = adverse event, N = number in analysis population, n = number of patients with event / in category, SAF = Safety Analysis Set.

12.6.8 Adverse Events and Adverse Drug Reactions in the PSAF Population

Overview summaries of AEs by category and hemophilia status reported in this study are provided in the Sections 12.6.8.1 to 12.6.8.5 for the total PSAF population and by subgroups, previous treatment, severity and outcome.

12.6.8.1 Summary of Adverse Events in the Total PSAF by Hemophilia A Status

An overall summary table of patients with AEs by category is provided in Table 53 for the PSAF population (Appendix Table 14.5.1.1.2).

In the total PSAF, overall 788 AEs occurred in 41 (85.4%) patients. Of these, 785 AEs occurred in 40 (85.1%) patients of the “Severe” subgroup and 3 AEs in 1 (100%) patient of the “Non-severe” subgroup (Appendix Table 14.5.1.2.2).

In the total PSAF, 120 AEs in 31 (64.6%) patients were considered serious (SAEs). All of these 120 SAEs occurred in 31 (66.0%) patients of the “Severe” subgroup (Appendix Table 14.5.1.3.2).

In the total PSAF, 585 AESIs occurred in 29 (60.4%) patients. Of these, 584 AESIs occurred in 28 (59.6%) patients of the “Severe” subgroup and 1 AESI in 1 (100%) patient of the “Non-severe” subgroup. In the total PSAF, 3 AESIs in 3 (6.3%) patients were serious (SAESIs; Appendix Table 14.5.1.8.2). Of these, all 3 SAESIs occurred in 3 (6.4%) patients of the “Severe” subgroup. In this summary, the term “AESI” refers to the definition in the observation plan, namely bleeding episodes, alongside the categories of thromboembolic

events, hypersensitivity / anaphylactic reactions, development of anti-FVIII inhibitors and transmission of infective agents subsequently defined in the SAP (v1.0, 25-Jan-2023). The numbers shown here are a combination of all these AE categories. In the detailed presentation below, the AE categories are presented separately.

- Overall, 581 AESIs of the category of bleeding were reported in 28 (58.3%) patients. Of these, 580 AESIs occurred in 27 (57.4%) patients of the “Severe” subgroup and 1 AESI in 1 (100%) patient of the “Non-severe” subgroup (Appendix Table 14.5.1.6.2). None of these AESIs were serious (Appendix Table 14.5.1.8.2).
- Overall, 2 AEs of the category of thromboembolic events were reported in 2 (4.2%) patients. Of these, both AEs occurred in 2 (4.3%) patients of the “Severe” subgroup (Appendix Table 14.5.1.6.2). Both of these AEs were serious (Appendix Table 14.5.1.8.2).
- Overall, 2 AEs of the category of hypersensitivity / anaphylactic reactions were reported in 2 (4.2%) patients. Of these, both AEs occurred in 2 (4.3%) patients of the “Severe” subgroup (Appendix Table 14.5.1.6.2). One of these AEs was serious (Appendix Table 14.5.1.8.2).
- In the total PSAF, no AEs of the categories of development of anti-FVIII inhibitor or transmission of infective agents were experienced by the patients (Appendix Table 14.5.1.6.2).

None of the AEs were assessed by the investigators to be related to Haemoctin SDH. Therefore, no ADRs, no SADRs, no related AESIs and no related SAESIs were documented for the PSAF.

Four AEs in 1 (2.1%) patient of the total PSAF resulted in death. This patient belonged to the “Severe” subgroup. The investigator assessed these 4 fatal AEs to be not related to Haemoctin SDH, and it was not possible to ascertain which of the 4 events was the actual cause of death (Appendix Table 14.5.1.10.2).

In the total PSAF, 2 AEs in 2 (4.2%) patients led to discontinuation of Haemoctin SDH. Both of these AEs occurred in 2 (4.3%) patients of the “Severe” subgroup. The 2 AEs leading to discontinuation of Haemoctin SDH were judged by the investigators not to be related to Haemoctin SDH (Appendix Table 14.5.1.11.2).

Table 53 Summary of adverse events (PSAF)

Type of AE	Hemophilia status								
	Severe (N=47)			Non-severe (N=1)			Total (N=48)		
	n	%	events	n	%	events	n	%	events
All Adverse events (AEs)	40	85.1	785	1	100.0	3	41	85.4	788
Serious adverse events (SAEs)	31	66.0	120	0	0.0	0	31	64.6	120
Adverse drug reactions (ADRs)	0	0.0	0	0	0.0	0	0	0.0	0
Serious adverse drug reactions (SADRs)	0	0.0	0	0	0.0	0	0	0.0	0
Adverse events of special interest (AESIs)*	28	59.6	584	1	100.0	1	29	60.4	585
Related Adverse events of special interest (Related AESIs)*	0	0.0	0	0	0.0	0	0	0.0	0
Serious adverse events of special interest (SAESIs)*	3	6.4	3	0	0.0	0	3	6.3	3
Related Serious adverse events of special interest (Related SAESIs)*	0	0.0	0	0	0.0	0	0	0.0	0
AEs resulting in death	1	2.1	4	0	0.0	0	1	2.1	4
AEs leading to discontinuation of Haemoctin SDH	2	4.3	2	0	0.0	0	2	4.2	2

Source: Appendix Table 14.5.1.1.2

N = number in analysis population, n = number of patients with event / in category, PSAF = Pooled Safety Analysis Set.

* In this table, the term AESI refers to the definition in the observation plan, namely bleeding episodes, alongside the categories of thromboembolic events, hypersensitivity / anaphylactic reactions, development of anti-FVIII inhibitors and transmission of infective agents subsequently defined in the SAP (v1.0, 25-Jan-2023). The numbers shown here are a combination of all these AE categories. In the detailed presentation below, the AE categories are presented separately.

12.6.8.2 Summary of Adverse Events in PSAF Subgroups by Treatment Regimen

An overall summary of patients with AEs by treatment regimen is provided in Table 54 for the PSAF population.

In the subgroup “Prophylaxis” (N=47), 770 AEs occurred in 40 (85.1%) patients. The occurrence of all types of AEs was similar to the total PSAF, which was expected due to the large overlap of patients between the two groups.

The proportion of patients with AEs of all AE categories in the small subgroups “Prophylaxis <20 IU/kg 3 times per week” (N=6; 264 AEs in 6 [100%] patients) and “Prophylaxis ≥20 IU/kg 3 times per week” (N=12; 65 AEs in 12 [100%] patients) were mostly similarly high.

Table 54 Summary of adverse events in subgroups by treatment regimen (PSAF)

Subgroup: Type of AE	Hemophilia status: Severe (N=47)			Non-severe (N=1)			Total (N=48)		
	n	%	events	n	%	events	n	%	events
Prophylaxis	(N=46)			(N=1)			(N=47)		
All Adverse events (AEs)	39	84.8	767	1	100.0	3	40	85.1	770
Serious adverse events (SAEs)	31	67.4	120	0	0.0	0	31	66.0	120
Adverse events of special interest (AESIs)*	27	58.7	568	1	100.0	1	28	59.6	569
Serious adverse events of special interest (SAESIs)*	3	6.5	3	0	0.0	0	3	6.4	3
AEs resulting in death	1	2.2	4	0	0.0	0	1	2.1	4
AEs leading to discontinuation of Haemoctin SDH	2	4.3	2	0	0.0	0	2	4.3	2
Prophylaxis <20 IU/kg 3 times per week	(N=5)			(N=1)			(N=6)		
All Adverse events (AEs)	5	100.0	261	1	100.0	3	6	100.0	264
Serious adverse events (SAEs)	4	80.0	13	0	0.0	0	4	66.7	13
Adverse events of special interest (AESIs)*	5	100.0	225	1	100.0	1	6	100.0	226
Serious adverse events of special interest (SAESIs)*	0	0.0	0	0	0.0	0	0	0.0	0
AEs resulting in death	0	0.0	0	0	0.0	0	0	0.0	0
AEs leading to discontinuation of Haemoctin SDH	1	20.0	1	0	0.0	0	1	16.7	1
Prophylaxis ≥20 IU/kg 3 times per week	(N=12)			(N=0)			(N=12)		
All Adverse events (AEs)	12	100.0	65				12	100.0	65
Serious adverse events (SAEs)	9	75.0	33				9	75.0	33
Adverse events of special interest (AESIs)*	7	58.3	21				7	58.3	21
Serious adverse events of special interest (SAESIs)*	1	8.3	1				1	8.3	1
AEs resulting in death	1	8.3	4				1	8.3	4
AEs leading to discontinuation of Haemoctin SDH	1	8.3	1				1	8.3	1

Source: Appendix Table 14.5.1.1.2.1

N = number in analysis population, n = number of patients with event / in category, PSAF = Pooled Safety Analysis Set.

* In this table, the term AESI refers to the definition in the observation plan, namely bleeding episodes, alongside the categories of thromboembolic events, hypersensitivity / anaphylactic reactions, development of anti-FVIII inhibitors and transmission of infective agents subsequently defined in the SAP (v1.0, 25-Jan-2023). The numbers shown here are a combination of all these AE categories. In the detailed presentation below, the AE categories are presented separately.

No AEs were judged by the investigators to be related; therefore, the corresponding AE categories are omitted in this table.

12.6.8.3 Summary of Adverse Events in PSAF Subgroups by Previous Treatment

An overall summary of AEs by previous treatment is shown in Table 55.

In the PTPs (N=39), 684 AEs occurred in 33 (84.6%) patients. The occurrence of all types of AEs was similar to the total PSAF, which was expected due to the relatively large overlap of patients between the two groups. The proportion of patients with the various types of AEs in the smaller subgroup of PUPs (N=9) was partly higher and partly lower; it was lower in the relatively low proportion of patients with AESIs in the total PSAF (i.e., 55.6% of patients compared with 61.5% of patients in the PTPs and 60.4% of patients in the PSAF).

Table 55 Summary of adverse events in subgroups by previous treatment (PSAF)

Subgroup: Type of AE	Hemophilia status: Severe (N=47)			Non-severe (N=1)			Total (N=48)		
	n	%	events	n	%	events	n	%	events
PUPs	(N=9)			(N=0)			(N=9)		
All Adverse events (AEs)	8	88.9	104				8	88.9	104
Serious adverse events (SAEs)	6	66.7	28				6	66.7	28
Adverse events of special interest (AESIs)*	5	55.6	61				5	55.6	61
Serious adverse events of special interest (SAESIs)*	1	11.1	1				1	11.1	1
AEs resulting in death	0	0.0	0				0	0.0	0
AEs leading to discontinuation of Haemoctin SDH	0	0.0	0				0	0.0	0
PTPs	(N=38)			(N=1)			(N=39)		
All Adverse events (AEs)	32	84.2	681	1	100.0	3	33	84.6	684
Serious adverse events (SAEs)	25	65.8	92	0	0.0	0	25	64.1	92
Adverse events of special interest (AESIs)*	23	60.5	523	1	100.0	1	24	61.5	524
Serious adverse events of special interest (SAESIs)*	2	5.3	2	0	0.0	0	2	5.1	2
AEs resulting in death	1	2.6	4	0	0.0	0	1	2.6	4
AEs leading to discontinuation of Haemoctin SDH	2	5.3	2	0	0.0	0	2	5.1	2

Source: Appendix Table 14.5.1.1.2.2

N = number in analysis population, n = number of patients with event / in category, PTP = previously treated patient, PUP = previously untreated patient, PSAF = Pooled Safety Analysis Set.

* In this table, the term AESI refers to the definition in the observation plan, namely bleeding episodes, alongside the categories of thromboembolic events, hypersensitivity / anaphylactic reactions, development of anti-FVIII inhibitors and transmission of infective agents subsequently defined in the SAP (v1.0, 25-Jan-2023). The numbers shown here are a combination of all these AE categories. In the detailed presentation below, the AE categories are presented separately.

No AEs were judged by the investigators to be related; therefore, the corresponding AE categories are omitted in this table.

12.6.8.4 Summary of Adverse Events by Severity (PSAF)

Among the overall 788 AEs in the total PSAF, the majority was mild (537 AEs in 29 [60.4%] patients), followed by 97 moderate AEs in 17 (35.4%) patients and 18 severe AEs in 12 (25.0%) patients (severity not available for 136 AEs in 34 [70.8%] patients) (Table 56).

Table 56 Summary of adverse events by severity (PSAF)

Severity of AE	Hemophilia status								
	Severe (N=47)			Non-severe (N=1)			Total (N=48)		
	n	%	events	n	%	events	n	%	events
Mild AEs	28	59.6	536	1	100.0	1	29	60.4	537
Moderate AEs	17	36.2	97	0	0.0	0	17	35.4	97
Severe AEs	12	25.5	18	0	0.0	0	12	25.0	18
Severity not available	33	70.2	134	1	100.0	2	34	70.8	136

Source: Appendix Table 14.5.1.2.2.2

AE = adverse event, N = number in analysis population, n = number of patients with event / in category, PSAF = Pooled Safety Analysis Set.

12.6.8.5 Summary of Adverse Events by Outcome (PSAF)

Among the overall 788 AEs in the total PSAF, the majority had the outcome “recovered/resolved” (731 AEs in 38 [79.2%] patients), followed by 18 AEs in 14 (29.2%) patients with the outcome “recovering/resolving”, 11 AEs in 8 (16.7%) patients with the outcome “not recovered / not resolved”, 11 AEs in 6 (12.5%) patients with the outcome “resolved with sequelae” and 4 fatal AEs in 1 (2.1%) patient (outcome unknown for 12 AEs in 6 [12.5%] patients; outcome not documented for 1 AE in 1 [2.1%] patient) (Table 57).

Table 57 Summary of adverse events by outcome (PSAF)

Outcome of AE	Hemophilia status								
	Severe (N=47)			Non-severe (N=1)			Total (N=48)		
	n	%	events	n	%	events	n	%	events
Recovered/resolved	37	78.7	729	1	100.0	2	38	79.2	731
Resolved with sequelae	6	12.8	11	0	0.0	0	6	12.5	11
Recovering/resolving	13	27.7	17	1	100.0	1	14	29.2	18
Fatal	1	2.1	4	0	0.0	0	1	2.1	4
Not recovered / not resolved	8	17.0	11	0	0.0	0	8	16.7	11
Unknown	6	12.8	12	0	0.0	0	6	12.5	12
Outcome not documented	1	2.1	1	0	0.0	0	1	2.1	1

Source: Appendix Table 14.5.1.2.2.3

AE = adverse event, N = number in analysis population, n = number of patients with event / in category, PSAF = Pooled Safety Analysis Set.

13. DISCUSSION

This non-interventional, retrospective and prospective, single-arm, uncontrolled, multi-center, international, post marketing authorization study observed treatments with Haemoctin SDH from November 2016 until December 2022. Considering a previous study, the total observation time covers a period of up to about 24 years. Thus, the present study expands the database on long-term use of Haemoctin in patients with hemophilia A under routine conditions in an international study population including Germany, Hungary and Austria.

The primary objective of the study was to evaluate the ABR in patients with Haemoctin SDH treatment, differentiated by prophylaxis and on demand treatment. The secondary objectives were to evaluate the occurrence and to characterize FVIII inhibitors, to evaluate the patients' QoL and to assess the frequency, severity, seriousness and causality of AEs.

Subgroups included hemophilia status at baseline (severe vs. non-severe), treatment regimen (patients on prophylaxis overall, patients on prophylaxis <20 IU / 3 times per week, patients on prophylaxis ≥20 IU / 3 times per week, and patients with on demand treatment; switchers between prophylaxis and on demand treatment did not participate), previous treatment (PUPs vs. PTPs) and country (Germany, Hungary, Austria). Subgroups were analyzed to identify possible differences between patient groups.

13.1 Key Results

Study Population

- Overall, 84 patients were enrolled in this NIS (APS), 41 in Germany, 37 in Hungary and 6 in Austria. The SAF, used for most analyses, included 80 patients. All patients included in the SAF were male. At baseline in the SAF, the median age was 38 years (range 2 to 81 years). The median age at diagnosis of hemophilia A was 1 year (range 9 to 70 years) and the median time since hemophilia A diagnosis was 35.5 years (range 0 to 75 years). At the beginning of the NIS, 8 patients had FVIII inhibitors and 72 patients had no FVIII inhibitors. The pooled population of the previous and current NIS (PSAF) included 48 patients

Treatment

- Nowadays, prophylaxis with FVIII products is more common than on demand treatment. Accordingly, the predominant treatment regimen in the NIS was "prophylaxis overall" (75/80 patients), while only 3/80 patients received on demand treatment. Data on the treatment regimen were missing for the remaining 2 patients. Within the prophylaxis group, 26/75 patients received "Prophylaxis ≥20 IU/kg 3 times per week" and 14/75 "Prophylaxis <20 IU/kg 3 times per week". The remaining 35 patients did not receive one of these two specific prophylaxis regimens. No major differences in treatment were observed between the

participating countries. Likewise, in the PSAF, 47/48 patients received prophylactic treatment and only 1/48 patient on demand treatment.

- In every treatment year, the most common frequency of injections was “3 times a week”.

Effectiveness

- Based solely on the Joint-Bleeds eCRF instrument, patients had a median ABR of 0.12 (FAS). The median ABR in the “Prophylaxis <20 IU/kg 3 times/week” subgroup was higher than in the “Prophylaxis ≥20 IU/kg 3 times/week” subgroup (2.47 vs. 0.0). The median ABR of PUPs and of PTPs was identical (0.24).
- Based on the eCRF Bleeding Page that included all types of bleeding, patients had a median extended ABR of 0.72 (FAS). The median extended ABR in the “Prophylaxis <20 IU/kg 3 times/week” subgroup was higher than in the “Prophylaxis ≥20 IU/kg 3 times/week” subgroup (2.67 vs. 0.87). The median extended ABR of PUPs was lower than of PTPs (0.24 vs. 0.88).
- In the previous study (Biotest NIS-013), patients had a mean±SD ABR of 13.3±16.6 (median: 6.1). However, the median ABR was considerably lower for patients who were treated prophylactically (3.2) compared with patients treated on demand (24.5) and the median ABR for all patients decreased over time (1998 to 2002: 20.7; 2003 to 2007: 9.4; 2008 to 2012: 5.2; 2013 to 2015: 2.6). Considering the predominant prophylactic treatment and the observed trend to improved ABRs in the past decades, the bleeding rates in the current NIS are in line with the previous NIS.
- In the total PSAF including patient data from the previous NIS, the mean±SD ABR was remarkably high with 18.7±18.3 (median: 13.3).
- Formation of FVIII inhibitors was not observed during the present study. No ITI was needed.
- Quality of life, assessed using the patient questionnaires Euroqol EQ-5D in adults and EQ-5D-Y in adolescents, did not reveal changes in most domains during treatment Years 1 to 3 (numbers of completed questionnaires were low during treatment Years 4 to 5). Only the VAS suggested a mild improvement in patient-reported health in Year 1 and 2 (SAF).
- The assessments of treatment effectiveness, tolerance and handling of Haemoctin SDH by the investigators and by the patients for the SAF was predominantly “very good” or “good” at every end of year documentation. Likewise, the investigators’ and patients’ assessment of patient health in the SAF was predominantly “very good” or “good” at every visit.

Safety

- Overall, 913 AEs were reported in 59 (73.8%) patients in the SAF. Of these, 893 AEs occurred in 52 (72.2%) patients of the “Severe” subgroup and only 20 AEs in 7 (87.5%) patients of the “Non-severe” subgroup.

- The majority of the 913 AEs was mild (666 AEs in 50 [62.5%] patients), followed by 173 moderate AEs in 34 (42.5%) patients and 28 severe AEs in 17 (21.3%) patients.
- The vast majority of the 913 AEs had the outcome “recovered/resolved” (814 AEs in 54 [67.5%] patients).
- Remarkably, none of the AEs were judged by the investigators to be related to Haemoctin SDH. So, no ADRs, no serious ADRs, no related AESIs and no related serious AESIs were documented in the present study.
- The most frequently documented preferred terms of AEs were “Haemarthrosis” (in 18 [22.5%] patients, 180 events; SOC “Musculoskeletal and connective tissue disorders”), “Spontaneous haemorrhage” (in 14 [17.5%] patients, 217 events; SOC “Blood and lymphatic system disorders”), “Haemorrhage” (in 13 [16.3%] patients, 295 events; SOC “Vascular disorders”), “Arthralgia” (in 9 [11.3%] patients, 12 events; SOC “Musculoskeletal and connective tissue disorders”) and “Traumatic haemorrhage” (in 9 [11.3%] patients, 15 events; SOC “Injury, poisoning and procedural complications”).
- In total, 52 SAEs in 23 (28.8%) patients were reported. Of these, 47 SAEs occurred in 20 (27.8%) patients of the “Severe” subgroup and 5 SAEs in 3 (37.5%) patients of the “Non-severe” subgroup.
- The most frequently documented preferred terms of SAEs were “Haemophilic arthropathy” (in 3 [3.8%] patients, 4 events; SOC “Musculoskeletal and connective tissue disorders”), “Osteoarthritis” (in 2 [2.5%] patients, 2 events; SOC “Musculoskeletal and connective tissue disorders”) and “Arthritis bacterial” (in 2 [2.5%] patients, 2 events; SOC “Infections and infestations”).
- AESIs were defined as bleeding episodes in general and of high relevance, including AEs resulting in bleeding. In the total SAF, 756 AESIs occurred in 48 (60.0%) patients, of which none was assessed as related by the investigators nor attributed to a suspected lack of efficacy or the development of FVIII inhibitors. Of these AESIs, 747 occurred in 44 (61.1%) patients of the “Severe” subgroup and 9 AESIs in 4 (50.0%) patients of the “Non-severe” subgroup. The most common AESIs in the SAF subgroup “Prophylaxis <20 IU/kg 3 times per week” (N=14) were “Haemarthrosis” (in 8 [57.1%] patients, 130 events; SOC “Musculoskeletal and connective tissue disorders”) and “Haemorrhage” (in 8 [57.1%] patients, 170 events; SOC “Vascular disorders”). The most common AESIs in the SAF subgroup “Prophylaxis ≥20 IU/kg 3 times per week” (N=26) were “Traumatic haemorrhage” (in 5 [19.2%] patients, 6 events; SOC “Injury, poisoning and procedural complications”), “Spontaneous haemorrhage” (in 4 [15.4%] patients, 16 events; SOC “Blood and lymphatic system disorders”) and “Haemarthrosis” (in 4 [15.4%] patients, 23 events; SOC “Musculoskeletal and connective tissue disorders”).
- 4 AEs of the type “Thromboembolic events” occurred in 4 (5.0%) patients. All of the reported events (“Stress cardiomyopathy”, “Post procedural myocardial infarction”,

"Paraparesis" and "Thrombophlebitis") were reported as serious and none of these events were assessed as related to Haemoctin SDH.

- Overall, 10 AEs of the type "Hypersensitivity / Anaphylactic reactions" occurred in 8 (10.0%) patients. All of the reported events ("Localised oedema", "Chest discomfort", "Swelling", "Cough", "Dermatitis", "Urticaria") were reported as non-serious and none of these events were assessed as related to Haemoctin SDH.
- No AEs of the types "Development of anti-FVIII inhibitors" and "Transmission of infective agents" were reported in the study.
- 4 AEs in 1 (1.3%) patient of the SAF resulted in death. The 4 fatal AEs were judged by the investigator not to be related to Haemoctin SDH. This patient was included in the SAF, the PSAF and in the following subgroups: hemophilia status "Severe"; treatment regimen "Prophylaxis" and "Prophylaxis ≥20 IU/kg 3 times per week"; previous treatment "PTPs".
- 4 AEs in 4 (5.0%) patients of the SAF led to discontinuation of Haemoctin SDH. The 4 AEs leading to discontinuation of Haemoctin SDH were judged by the investigators not to be related to Haemoctin SDH.

13.2 Limitations

- High rate of premature study termination: In the SAF, 58 (72.5%) patients did not complete the study but terminated prematurely. The main reason was a switch from Haemoctin SDH to a different FVIII product, mostly a plasma product or recombinant product. Consequently, the number of patients with data at later time points, particularly Year 4 and 5, were reduced.
- Different sizes of subgroups of the SAF, e.g., for hemophilia status ("Severe", N=72; "Non-severe", N=8) or treatment regimen ("Prophylaxis overall", N=75; "on demand", N=3; not known for 2 patients) impair a meaningful comparison of subgroups. The patients in the large subgroups ("Severe" and "Prophylaxis overall") were generally identical to the SAF except for only a few patients and the results were therefore almost identical in those groups. By contrast, in the small subgroups, changes in individual patients strongly influenced the average values, leading to stronger deviations from the SAF.
- Small and different sizes of subgroups of specific prophylactic treatment: Among the 75 patients in the SAF who received prophylactic treatment, 26 (32.5%) patients received "≥20 IU/kg 3 times per week", 14 (17.5%) received "<20 IU/kg 3 times per week" and the remaining 35 patients did not receive one of these two specific prophylaxis regimens and were not evaluated as a subgroup. Again, the small and different sizes of the subgroups hinder the comparison.
- Relatively small size of the PSAF: The previous NIS analyzed 163 patients and the present NIS 80 patients. Only 48 patients were included in the combined analysis of

both studies (PSAF). With 33 patients a large proportion of the patients of the present NIS were excluded from the PSAF because they were not treated in the previous NIS.

- AEs that resulted in bleeding events (e.g., accidents, surgeries, and trauma) were not consequently reported by the investigators. In consequence, the explanations for the bleeding events are mostly missing (spontaneous vs. trauma associated). Similarly, it is not known whether patients, over time, experienced an increased tendency to bleed or a higher demand for Haemoctin SDH (prophylactic) treatment due to factors such as lifestyle changes (i.e., exercise).

13.3 Interpretation and Discussion

Patients included in the study exhibited a general predisposition to bleeding which, amongst others, was attributed to the severe phenotype of 72/80 patients, the presence of existing hemophilic arthropathy with pre-damaged joints (tertiary prophylaxis was the leading regimen), accidents, surgeries, trauma, obesity, liver diseases and/or an inadequate prophylaxis (lower dose and/or less frequently than recommended by the currently valid SmPC).

The comparison of prophylaxis regimens, "<20 IU/kg 3 times per week" and “≥20 IU/kg 3 times per week,” revealed notable differences in the occurrence of AEs associated with the underlying disease. Despite the limitations posed by the relatively low number of patients, a clear trend emerged, with a higher incidence of bleeding events in patients receiving the "<20 IU/kg 3 times per week" regimen. This aligns with the anticipated outcomes considering the SmPC recommendation for Haemoctin SDH prophylaxis.

From the study results, recommendations for patient management may be drawn, highlighting the need for tailored approaches based on individual patient characteristics and adherence to recommended prophylaxis regimens. Recognizing the challenges posed by the underlying disease, particularly in patients with severe hemophilia, emphasizes the importance of a proactive and personalized therapeutic strategy.

Overall, the results of the present study are in line with the results of the previous study. Again, expectations of the MAH and the investigators were met. Both, investigators and patients provided high ratings of treatment effectiveness, tolerance and handling of Haemoctin SDH in daily life.

No new and formerly unknown information with regard to the safety of Haemoctin SDH became apparent in this NIS, even more so as no AE was judged by the investigators to be related to Haemoctin SDH.

13.4 Generalizability

Patients documented in this NIS at 11 German and 7 Hungarian hemophilia centers and 1 Austrian hemophilia center (with 2 sub-centers, i.e., children and adults) can be regarded as representative for hemophilia A patients living in the EU, at least for Caucasian patients. Except for 4 patients, all patients were Caucasian (76/80 patients). One of the non-Caucasian patients was Asian and 3 were “Other”.

14. OTHER INFORMATION

None.

15. CONCLUSION

Overall, 80 patients with hemophilia A treated with Haemoctin SDH under everyday clinical practice conditions were observed between November 2016 and December 2022. The ABR based on the Joint-Bleeds eCRF instrument or on the eCRF Bleeding Page was low with a median ABR of 0.12 and 0.72, respectively. This bleeding rate was lower than in the previous NIS, reflecting the change from on demand treatment to the more effective prophylactic treatment in the past decades. The low bleeding rates indicate an effective management of hemophilia A.

The assessments of treatment effectiveness, tolerance and handling of Haemoctin SDH by the investigators and by the patients for the SAF was predominantly “very good” or “good” at every end of year documentation. Likewise, the investigators’ assessment of the patients’ health in the SAF was predominantly “very good” or “good” at every visit.

Overall, treatment with Haemoctin SDH was well tolerated. No new and formerly unknown information with regard to the safety and tolerability of Haemoctin was reported during the study period. No AEs were judged to be related to Haemoctin SDH. Formation of FVIII inhibitors was not observed during the entire study.

The study results confirm the positive benefit-risk profile of Haemoctin in the indication and prophylaxis of bleeding in patients with hemophilia A. The benefit-risk profile of Haemoctin remains clearly favorable.

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17. APPENDICES

17.1 Appendix 1. List of Stand-Alone Documents

Appendix number	Date	Title
1.1	18-Feb-2021	Haemoctin NIS Observation Plan, version 2.0
1.2	25-Jan-2023	BT13218 Biotest NIS-016 Haemoctin SDH_SAP Final v1.0
1.3	31-May-2023	BT13218_DRM_Minutes_v1.0_Final_31-05-2023
1.4	-	List of study sites in Germany, Hungary and Austria
1.5	04-Dec-2023	BT13218_Final_Analysis_Tables_Final_v2.0_20231204
1.6	04-Dec-2023	BT13218_Final_Analysis_Listings_Final_v2.0_20231204
1.7	04-Dec-2023	BT13218_Final_Analysis_Figures_Final_v2.0_20231204

17.2 Appendix 2. All Adverse Events in the Global PV Database

MedDRA Version 26.0 Haemoctin SDH; Biotest NIS-16						
System Organ Class Preferred Term	Serious AEs	Patient No.	Non-Serious AEs	Patient No.	Total AEs	Total Patient No.
Musculoskeletal and connective tissue disorders	**98**	**17**	**522**	**35**	**620**	**40**
Haemophilic arthropathy	4	3	5	3	9	6
Haemarthrosis	84	12	484	29	568	32
Arthralgia	0	0	12	9	12	9
Muscle haemorrhage	3	2	5	5	8	7
Spondylolisthesis	1	1	0	0	1	1
Joint swelling	0	0	2	2	2	2
Pain in extremity	0	0	3	2	3	2
Synovitis	1	1	1	1	2	2
Myosclerosis	0	0	1	1	1	1
Osteoarthritis	2	2	2	2	4	4
Muscle atrophy	0	0	2	1	2	1
Spinal stenosis	1	1	0	0	1	1
Back pain	0	0	2	2	2	2
Muscle spasms	0	0	2	2	2	2
Soft tissue haemorrhage	1	1	0	0	1	1
Foot deformity	1	1	0	0	1	1
Joint effusion	0	0	1	1	1	1
Blood and lymphatic system disorders	**0**	**0**	**50**	**10**	**50**	**10**
Spontaneous haemorrhage	0	0	49	9	49	9
Iron deficiency anaemia	0	0	1	1	1	1
Surgical and medical procedures	**9**	**7**	**8**	**3**	**17**	**10**
Colostomy closure	1	1	0	0	1	1
Elective surgery	1	1	0	0	1	1
Knee arthroplasty	2	2	0	0	2	2
Umbilical hernia repair	1	1	0	0	1	1
Hernia repair	1	1	0	0	1	1
Skin lesion removal	1	1	0	0	1	1
Wisdom teeth removal	0	0	1	1	1	1
Arteriovenous fistula operation	1	1	1	1	2	2
Tooth extraction	1	1	5	1	6	2
Radiotherapy to joint	0	0	1	1	1	1
Injury, poisoning and procedural complications	**17**	**9**	**62**	**19**	**79**	**23**
Joint injury	0	0	1	1	1	1
Traumatic haemorrhage	6	2	25	13	31	15
Traumatic fracture	1	1	0	0	1	1
Injury	0	0	1	1	1	1
Fall	3	3	18	5	21	6

MedDRA Version 26.0 Haemoctin SDH; Biotest NIS-16 System Organ Class Preferred Term	Serious AEs	Patient No.	Non-Serious AEs	Patient No.	Total AEs	Total Patient No.
Meniscus injury	1	1	0	0	1	1
Contusion	0	0	5	4	5	4
Wound	0	0	2	2	2	2
Alcohol poisoning	1	1	0	0	1	1
Traumatic haematoma	0	0	4	3	4	3
Incisional hernia	1	1	0	0	1	1
Periprosthetic fracture	1	1	0	0	1	1
Femur fracture	1	1	0	0	1	1
Radius fracture	1	1	0	0	1	1
Limb injury	0	0	2	2	2	2
Bite	0	0	1	1	1	1
Post procedural myocardial infarction	1	1	0	0	1	1
Limb crushing injury	0	0	1	1	1	1
Procedural haemorrhage	0	0	1	1	1	1
Post procedural haemorrhage	0	0	1	1	1	1
Renal and urinary disorders	**3**	**1**	**6**	**3**	**9**	**4**
Haematuria	1	1	6	3	7	4
Pollakiuria	1	1	0	0	1	1
Urinary retention	1	1	0	0	1	1
Gastrointestinal disorders	**10**	**7**	**21**	**10**	**31**	**15**
Diverticulum intestinal	1	1	0	0	1	1
Large intestine perforation	1	1	0	0	1	1
Gastrointestinal motility disorder	1	1	0	0	1	1
Abdominal hernia	1	1	0	0	1	1
Barrett's oesophagus	1	1	0	0	1	1
Gingival bleeding	0	0	2	2	2	2
Gastritis	1	1	0	0	1	1
Toothache	0	0	1	1	1	1
Intra-abdominal haemorrhage	0	0	1	1	1	1
Dental caries	0	0	6	2	6	2
Dental discomfort	0	0	1	1	1	1
Mouth haemorrhage	0	0	2	2	2	2
Pancreatic disorder	1	1	0	0	1	1
Umbilical hernia	2	2	0	0	2	2
Abdominal discomfort	0	0	1	1	1	1
Haematochezia	0	0	1	1	1	1
Rectal haemorrhage	0	0	1	1	1	1
Intra-abdominal haematoma	0	0	1	1	1	1
Haemorrhoidal haemorrhage	0	0	2	1	2	1
Loose tooth	1	1	0	0	1	1

MedDRA Version 26.0 Haemoctin SDH; Biotest NIS-16 System Organ Class Preferred Term	Serious AEs	Patient No.	Non-Serious AEs	Patient No.	Total AEs	Total Patient No.
Noninfective sialoadenitis	0	0	1	1	1	1
Oral disorder	0	0	1	1	1	1
Infections and infestations	**12**	**6**	**18**	**11**	**30**	**16**
Peritonitis	1	1	0	0	1	1
Tonsillitis	0	0	4	4	4	4
Infection	0	0	1	1	1	1
Upper respiratory tract infection	0	0	1	1	1	1
Paronychia	0	0	1	1	1	1
Febrile infection	0	0	1	1	1	1
Gingivitis	0	0	1	1	1	1
Pneumonia	1	1	1	1	2	2
Erysipelas	0	0	1	1	1	1
Periodontitis	0	0	1	1	1	1
Influenza	1	1	0	0	1	1
Pneumonia bacterial	1	1	0	0	1	1
Furuncle	0	0	1	1	1	1
Ear infection	0	0	1	1	1	1
COVID-19	0	0	2	2	2	2
Pilonidal disease	1	1	0	0	1	1
Diverticulitis	1	1	0	0	1	1
Arthritis bacterial	2	2	0	0	2	2
Cellulitis	1	1	0	0	1	1
Abscess	0	0	1	1	1	1
Catheter site infection	1	1	0	0	1	1
Viral infection	0	0	1	1	1	1
Epididymitis	1	1	0	0	1	1
Urinary tract infection	1	1	0	0	1	1
Vascular disorders	**5**	**5**	**48**	**16**	**53**	**17**
Hypertension	1	1	2	2	3	3
Haemorrhage	1	1	41	11	42	11
Haematoma	1	1	5	3	6	4
Vein disorder	1	1	0	0	1	1
Thrombophlebitis	1	1	0	0	1	1
Cardiac disorders	**3**	**3**	**0**	**0**	**3**	**3**
Atrial fibrillation	2	2	0	0	2	2
Stress cardiomyopathy	1	1	0	0	1	1
Eye disorders	**1**	**1**	**11**	**2**	**12**	**3**
Eye haemorrhage	1	1	6	1	7	2
Retinopathy hypertensive	0	0	1	1	1	1
Conjunctival haemorrhage	0	0	4	1	4	1

MedDRA Version 26.0 Haemoctin SDH; Biotest NIS-16 System Organ Class Preferred Term	Serious AEs	Patient No.	Non-Serious AEs	Patient No.	Total AEs	Total Patient No.
Respiratory, thoracic and mediastinal disorders	**2**	**2**	**30**	**10**	**32**	**11**
Epistaxis	1	1	24	6	25	6
Oropharyngeal pain	0	0	2	1	2	1
Respiratory failure	1	1	0	0	1	1
Nasal congestion	0	0	1	1	1	1
Cough	0	0	3	3	3	3
Skin and subcutaneous tissue disorders	**0**	**0**	**7**	**5**	**7**	**5**
Skin ulcer	0	0	1	1	1	1
Skin haemorrhage	0	0	3	1	3	1
Urticaria	0	0	1	1	1	1
Nail bed bleeding	0	0	1	1	1	1
Acne	0	0	1	1	1	1
General disorders and administration site conditions	**9**	**7**	**21**	**11**	**30**	**17**
Disease progression	3	2	1	1	4	2
Gait disturbance	0	0	1	1	1	1
Inflammation	1	1	1	1	2	2
Localised oedema	0	0	4	2	4	2
Peripheral swelling	0	0	2	2	2	2
Swelling	0	0	5	5	5	5
Mucosal haemorrhage	1	1	0	0	1	1
General physical health deterioration	1	1	1	1	2	2
Chest pain	0	0	1	1	1	1
Pain	0	0	2	2	2	2
Impaired healing	1	1	0	0	1	1
Pyrexia	0	0	3	2	3	2
Malaise	1	1	0	0	1	1
Multiple organ dysfunction syndrome	1	1	0	0	1	1
Investigations	**1**	**1**	**1**	**1**	**2**	**2**
Weight decreased	1	1	0	0	1	11
Blood potassium decreased	0	0	1	1	1	1
Nervous system disorders	**2**	**2**	**2**	**2**	**4**	**4**
Paraparesis	1	1	0	0	1	1
Headache	0	0	2	2	2	2
Status epilepticus	1	1	0	0	1	1
Psychiatric disorders	**1**	**1**	**0**	**0**	**1**	**1**
Depression	1	1	0	1	1	1
Social circumstances	**0**	**0**	**2**	**2**	**2**	**2**
Physical disability	0	0	2	2	2	2
Reproductive system and breast disorders	**2**	**1**	**0**	**0**	**2**	**1**
Prostatic haemorrhage	2	1	0	0	2	1

MedDRA Version 26.0 Haemoctin SDH; Biotest NIS-16						
System Organ Class Preferred Term	Serious AEs	Patient No.	Non-Serious AEs	Patient No.	Total AEs	Total Patient No.
Congenital, familial and genetic disorders	**1**	**1**	**1**	**1**	**2**	**2**
Factor II mutation	1	1	1	1	2	1
Metabolism and nutrition disorders	**1**	**1**	**1**	**1**	**2**	**2**
Hyperuricaemia	0	0	1	1	1	1
Propofol infusion syndrome	1	1	0	0	1	1
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**1**	**1**	**1**	**1**	**2**	**2**
Hepatocellular carcinoma	1	1	0	0	1	1
Melanocytic naevus	0	0	1	1	1	1
Totals	**178**	**36**	**812**	**52**	**990**	**59**

17.3 Appendix 3. Additional Information

None.