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Post-Authorization Safety Study (PASS) Year 2 Interim Analysis Report - Study Information

Acronym/Title	HA-SAFE: Observational study evaluating long-term safety of real-world treatment with damoctocog alfa pegol in previously treated patients with hemophilia A
Report version and date	v 1.0, 08 SEP 2023
IMPACT study number	20904
Study type / Study phase	Observational, post-approval PASS: ☒ YES ☐ NO Joint PASS: ☐ YES ☒ NO
EU PAS register number	EUPAS33520
NCT number	NCT04461639
Active substance	ATC code: B02BD02/Hematological/Damoctocog alfa pegol
Medicinal product / Medical Device / Combination Product	Jivi
Product reference	EU/1/18/1324/001 Jivi 250 IU; EU/1/18/1324/002 Jivi 500 IU; EU/1/18/1324/003 Jivi 1000 IU; EU/1/18/1324/004 Jivi 2000 IU; EU/1/18/1324/005 Jivi 3000 IU
Procedure number	EMEA/H/C/004054
Comparator / Reference therapy	Not applicable
Study Initiator and Funder	Bayer Consumer Care AG, Basel, Switzerland
Research question and objectives	The primary objective of this study is to assess the long-term safety of prophylaxis with damoctocog alfa pegol in patients with hemophilia A in the real-world setting through the collection and analysis of adverse events (AEs) of special interest including those potentially indicative of polyethylene

	glycol (PEG) accumulation (hypersensitivity reactions, loss of drug effect, renal impairment, neurocognitive disorders, and inhibitor development), AEs, serious AEs, and adverse reactions. The secondary objective is to monitor the clinical effects of long-term exposure of prophylaxis with damoctocog alfa pegol in patients with hemophilia A, including assessments of kidney and liver function parameters, neurological function and patients' PEG plasma levels.
Countries of study	The study will be conducted in Europe in the following countries: Germany, Italy, Spain, Austria, Slovenia and Greece. The study may also be conducted in other countries not currently listed.
Author	PPD MD Bayer Consumer Care AG, Basel, Switzerland

Marketing authorization holder

Marketing authorization holder(s)	Bayer AG, 51368 Leverkusen, Germany
MAH contact person	Dr. PPD Bayer AG, 42113 Wuppertal, Germany

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1. Abstract

Acronym/Title	HA-SAFE: Observational study evaluating long-term safety of real-world treatment with damoctocog alfa pegol in previously treated patients with hemophilia A
Report version and date **Author**	v 1.0, 08 SEP 2023 PPD MD Bayer consumer Care AG, Basel, Switzerland
IMPACT study number	20904
Keywords	Hemophilia A, damoctocog alfa pegol, real-world evidence, safety
Rationale and background	Hemophilia A is an X-linked, inherited, genetic bleeding disorder characterized by the deficiency of clotting factor VIII (FVIII). Hemophilia A comprises approximately 80% of all hemophilia cases, with an annual incidence of approximately 1 in 5,000 live male births. Damoctocog alfa pegol is approved for prophylaxis and treatment of bleeds in previously treated patients (PTPs) with hemophilia A aged ≥12 years, with a 2 times per week, every 5 days or every 7 days dose that allows for the treatment regimen to be tailored to individual patient needs. Efficacy and safety of prophylaxis dosing with damoctocog alfa pegol were demonstrated in 2 phase II/III clinical studies in adult, adolescent, and pediatric (<12 years of age) PTPs with severe hemophilia A. The aim of this observational study is to characterize in a real-world setting the long-term safety of damoctocog alfa pegol drug usage. Patients and physicians participating in HA-SAFE can choose from 3 effective prophylaxis regimens with damoctocog alfa pegol based on individual patient bleeding profile and lifestyle.
Research question and objectives	The primary objective of this study is: • To assess the long-term safety of prophylaxis with damoctocog alfa pegol in patients with hemophilia A in the real-world setting through the collection and analysis of adverse events (AEs) of special interest including those potentially indicative of polyethylene glycol (PEG) accumulation (hypersensitivity reactions, loss of drug effect, renal impairment, neurocognitive disorders, and inhibitor development), AEs, serious adverse events (SAEs), and adverse reactions (ARs).

	The secondary objective of this study is: • To monitor the clinical effects of long-term exposure of prophylaxis with damoctocog alfa pegol in patients with hemophilia A, including assessments of kidney and liver function parameters, neurological function and patients' PEG plasma levels.
Study design	This is a multinational, open-label, prospective, non-interventional, multicenter, cohort study of PTPs with hemophilia A receiving damoctocog alfa pegol as prophylaxis treatment.
Setting	The study will be conducted in multiple countries in Europe. Enrollment started on 14 MAY 2021. Follow-up visits occur during routine practice. After the initial visit, data collection will continue for a minimum of 48 months.
Subjects and study size, including dropouts	PTPs with hemophilia A receiving prophylaxis damoctocog alfa pegol with a negative FVIII inhibitor test will be eligible to be enrolled into the study. The study aims to observe 50 patients for at least 4 years each. Assuming a dropout rate of approximately 20% (due to lost to follow-up cases or withdrawals), 60 patients will be enrolled.
Variables and data sources	The physician collects historical study-relevant data (demographic and clinical characteristics) from medical records if available (or by interviewing the patient at the initial [baseline] visit) and treatment-related data during visits. Patient diaries will be provided to the patients, and they will be trained by the site personnel on how to complete them. Patient diaries will be reviewed for AEs at each visit.
Results	A total of 62 patients were enrolled, all of which have been included in the safety analysis set (SAF) with a median observation period of 213 days. Most patients (57 patients, 91.94%) were on prophylaxis with damoctocog alfa pegol for a median of 12 months before enrollment in the study. The most common treatment regimen was every 5 days (35.5%), twice weekly was reported in 14 cases (22.6%), whereas every 7 days was only reported in 3 cases (4.8%).

	All patients were male, the vast majority being White (87.10%) and coming from Germany (56.45%), Spain (17.74%), Greece (11.29%), Italy (9.68%) and Austria (4.84%). The mean ± SD age was 37.8 ± 13.94 years. Overall, 56 patients were diagnosed with severe hemophilia A and 6 patients with moderate hemophilia A. A total of 22 patients (35.48%) experienced 43 treatment-emergent adverse events (TEAEs) with 8 patients (12.90%) experiencing treatment-emergent serious adverse events (TESAEs). One event was drug-related and a TEAE of special interest (TEAESI) leading to loss of drug effect and inhibitor development, which was classified as serious and recovered without change in dose. There were no deaths. No TEAEs leading to discontinuation of damoctocog alfa pegol were reported. The majority of the reported TEAEs were of mild or moderate intensity (11 patients [17.74%] with maximum intensity of mild and 6 [9.68%] moderate) and were recovered/resolved or recovering/resolving at the time of this report. No adverse reaction was reported related to any of the secondary endpoints referring to nervous system and psychiatric disorders and renal and hepatic functions. Data regarding laboratory assessments are unclean, with some of the values being queried and are therefore to be interpreted with caution. In the majority of the patients with the reported laboratory values, no laboratory abnormalities were found. In a small number of patients, isolated laboratory values outside of the normal range were reported on single occasions, including at baseline. None of the laboratory values outside the normal range was reported as a TEAE. No safety concern has been identified based on the available data.
Discussion	At the time of this report 22 patients had experienced any TEAE. A total of 8 patients experienced a TESAE. With an exception of 1 TEAE, all reported TEAEs were assessed as unrelated to damoctocog alfa pegol. One TESAE of low titer factor VIII inhibitor development was reported, which was assessed as drug-related and was also a TEAESI. The event recovered without damoctocog alfa pegol discontinuation. The majority of the reported TEAEs were of mild or moderate intensity and were recovered/resolved or recovering/resolving at the time of this report. No TEAEs leading to discontinuation of damoctocog alfa pegol were reported and no indication of renal impairment or neurocognitive disorder was observed. Based on these results obtained from the HA-SAFE study, it can be concluded that damoctocog alfa

	pegol treatment is safe and well tolerated, thus confirming a positive benefit-risk ratio
Marketing Authorization Holder(s)	Bayer AG, 51368 Leverkusen, Germany.
Names and affiliations of principal investigators	Contact details of the principal and/or coordinating investigators for each country and site participating in the study are listed in a stand-alone document (see Annex 1), which is available upon request.

2. List of abbreviations

AE	Adverse Event
AG	*Aktiengesellschaft*
ALT	Alanine Aminotransferase
AR	Adverse Reaction
AST	Aspartate Aminotransferase
BU	Bethesda Units
BMI	Body Mass Index
COVID-19	Coronavirus Disease 2019
CRA	Clinical Research Associate
CRO	Contract Research Organization
CRP	C-Reactive Protein
DMP	Data Management Plan
DLP	Data Lock Point
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
eGFR	Estimated Glomerular Filtration Rate
EMA	European Medicines Agency
EU	European Union
EU PAS	European Union electronic Register of Post-Authorization Studies
FVIII	Factor VIII
FPFV	First Patient First Visit
GGT	Gamma-Glutamyl Transferase
IU	International Unit
MAH	Marketing Authorization Holder
Max	Maximum
MedDRA	Medical Dictionary for Regulatory Activities
Min	Minimum
MRP	Medical Review Plan
NCT	National Clinical Trial
NIS	Non-interventional Study
PASS	Post-Authorization Safety Study
PEG	Polyethylene Glycol
PK	Pharmacokinetics
PKAS	Pharmacokinetics Analysis Set
PRAC	Pharmacovigilance Risk Assessment Committee
PT	Preferred Term
PTP	Previously Treated Patient
QPPV	Qualified Person Responsible for Pharmacovigilance
QRP	Quality Review Plan
SAE	Serious Adverse Event

SAF	Safety Analysis Set
SAP	Statistical Analysis Plan
SD	Standard Deviation
SOC	System Organ Class
TEAE	Treatment-Emergent Adverse Event
TEAESI	Treatment-Emergent Adverse Event of Special Interest
TESAE	Treatment-Emergent Serious Adverse Event
TFL	Tables, Figures, Listings
U	Unit

3. Investigators

Contact details of the principal and/or coordinating investigators and co-investigators for each country and sites participating in the study are listed in a stand-alone document (see Annex 1), which is available upon request.

4. Other responsible parties

Sponsor contact names:

Role: PPD

Name: PPD PhD

E-mail: PPD

Role: PPD

Name: PPD MD

Role: Marketing authorization holder (MAH) contact person (Regulatory Affairs)

Name: PPD

Role: PPD

Name: PPD MD

Role: PPD

Name: PPD MD

Role: PPD

Name: PPD

Role: PPD

Name: PPD

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Name: PPD

Role: PPD

Name: PPD

Contact details are available upon request.

Contract research organization:

Contract research organization (CRO) contact details:

Cerner Enviza

Landsberger Straße 284, 80687 Munich, Germany

5. Milestones

Table 5-1: Milestones

Milestone	Planned date	Actual date	Comments
Start of data collection (FPFV)	Q2 2021	14 MAY 2021	
End of data collection (LPLV)	Q1 2027		
Registration in the EU PAS register	Q2 2020	18 JUN 2020	
Cut-off date for first interim analysis	16 MAY 2022	16 MAY 2022	
Year 1 Interim report	Q3 2022	29 SEP 2022	
Cut-off date for second interim analysis	05 MAY 2023	05 MAY 2023	
Year 2 Interim report	Q3 2023	08 SEP 2023	
Database Clean	Q2 2027		
Final report of study results	Q4 2027		

EU PAS: European Union electronic register of post-authorization studies, FPFV: first patient first visit, LPLV: last patient last visit.

6. Rationale and background

Hemophilia A is an X-linked, inherited, genetic bleeding disorder characterized by the deficiency of clotting factor VIII (FVIII). Hemophilia A comprises approximately 80% of all hemophilia cases, with an annual incidence of approximately 1 in 5,000 live male births. All races and economic groups are affected equally. Prevalence estimates vary by country, ranging between 5 and 21 cases per 100,000 male births (1, 2). Damoctocog alfa pegol is approved for prophylaxis and treatment of bleeds in previously treated patients (PTPs) with hemophilia A aged ≥12 years, with a 2 times per week, every 5 days or every 7 days dose that allows for the treatment regimen to be tailored to individual patient needs. Efficacy and safety of prophylaxis dosing with damoctocog alfa pegol were demonstrated in 2 phase II/III clinical studies in adult, adolescent, and pediatric (<12 years of age) PTPs with severe hemophilia A (3, 4). Outside of the clinical study, there are currently little real-world safety data on the use of the product. The aim of this observational study is to characterize in a real-world setting the long-term safety of damoctocog alfa pegol drug usage. Patients and physicians participating in HA-SAFE can choose from 3 effective prophylaxis regimens with damoctocog alfa pegol based on individual patient bleeding profile and lifestyle.

7. Research question and objectives

The primary objective of this study is:

- To assess the long-term safety of prophylaxis with damoctocog alfa pegol in patients with hemophilia A in the real-world setting through the collection and analysis of adverse

events (AEs) of special interest including those potentially indicative of polyethylene glycol (PEG) accumulation (hypersensitivity reactions, loss of drug effect, renal impairment, neurocognitive disorders, and inhibitor development), AEs, serious adverse events (SAEs), and adverse reactions (ARs).

The secondary objective of this study is:

- To monitor the clinical effects of long-term exposure of prophylaxis with damoctocog alfa pegol in patients with hemophilia A, including assessments of kidney and liver function parameters, neurological function and patients' PEG plasma levels.

8. Amendments and updates

Table 8-1: Amendments to the protocol

No.	Date	Section of study protocol	Amendment / Update	Reason
1	08 JUL 2020	6	Version 1.1	COVID-19 related update of study milestones.
2	08 JUL 2020	11.3, 3	Version 1.1	According to the PRAC agreement, the wording in section 11.3 on the event of loss of drug effect needs clarification to avoid the impression that anti-PEG antibodies need to be measured. The examples given in brackets such as immune response to PEG, anti-drug antibodies, etc. were deleted. Names of responsible people were updated.
3	25 MAY 2021	6, Abstract	Version 1.2	Milestone FPFV changed from Q4/2020 to Q2/2021. EU PAS register number was added. Names of responsible people were updated. Participating countries were added.

COVID-19: coronavirus disease 2019, EU PAS: European Union electronic register of post-authorization studies, FPFV: first patient first visit, PEG: polyethylene glycol, PRAC: Pharmacovigilance Risk Assessment Committee.

9. Research methods

9.1 Study design

This is a multinational, open-label, prospective, non-interventional, multicenter, cohort study of PTPs with hemophilia A receiving damoctocog alfa pegol as prophylaxis treatment. The study is conducted in multiple countries in Europe.

At study start, retrospective data will be collected on the patients' baseline characteristics (including genotyping [where available], medical condition, and hemophilia treatment history). Also, at study start and then at each physician visit during the follow-up phase, data will be recorded on regimens used, AEs of special interest including hypersensitivity reactions, loss of drug effect, renal impairment, neurocognitive disorders, inhibitor

development, other AEs, SAEs and drug-related ARs in standard clinical practice. If collected in routine clinical practice at the physician's discretion, parameters relating to kidney and liver function (e.g., creatinine, estimated glomerular filtration rate [eGFR], alanine aminotransferase [ALT], aspartate aminotransferase [AST], bilirubin), PEG plasma level and abnormal findings from neurological assessments will be captured in the electronic case report form (eCRF)/electronic data capture (EDC) system. ARs relating to the system organ classes (SOCs) of the nervous system and psychiatric disorders will be recorded.

Patients/legal representatives and physicians can choose from different prophylaxis regimens with damoctocog alfa pegol following approved local labels or any other regimen prescribed by the physician as part of normal clinical practice. Patients/legal representatives and physicians can choose to change the dosing regimen based on the patient's response to treatment at any time. A reason for the dose and/or frequency change should be documented.

The planned observation period for each of at least 50 patients will be a minimum of 48 months for the collection of long-term safety data and the prospective monitoring of clinical effects of long-term exposure of prophylaxis with damoctocog alfa pegol in PTPs with hemophilia A.

Due to the observational nature of the study, follow-up visits cannot be scheduled specifically for study purposes, and it is unknown when a patient will come for the next visit. Thus, data collection will occur continuously throughout the patient's observation period (i.e., each visit or assessment as well as AEs reported in the patient diary will be documented in the eCRF/EDC system as they occur). Data collection will continue after 48 months for those patients who are still within the overall study period (i.e., patients initiating follow-up in the first years of the study). Final data collection is planned after 50 patients have been followed-up for a minimum of 4 years. The study will then be terminated for all patients.

The primary endpoint is:

- Occurrence, duration, treatment, seriousness, and outcome of AEs, SAEs, ARs, and FVIII inhibitor from study start to end of study

The secondary endpoints are:

- Number of ARs that are defined within the SOCs nervous system and psychiatric disorders from study start to end of study
- Number of ARs related to hepatic or renal function from study start to the end of study
- Change in kidney and liver function parameters from study start to the end of study
- Change in PEG plasma levels from study start to the end of study
- Number of patients with abnormal findings as assessed by neurological examination across all age groups from study start to the end of study

9.2 Setting

The study will be conducted in multiple countries in Europe. Enrollment started on 14 MAY 2021.

The physician documents a first visit that corresponds to the initiation of the observation period (initial visit/baseline) in the eCRF/EDC system. Follow-up visits occur during routine practice. In this non-interventional study (NIS), the exact referral dates for those visits are not defined in the study protocol. After the initial visit, data collection will continue for a minimum of 48 months. Data collection will continue after 48 months for those patients who

are still within the overall study period (for patients initiating follow-up in the first years of the study). Each visit or assessment, as well as each AE, recorded in the patient diary is to be documented in the eCRF/EDC system. The data to be collected, where they are available as part of routine practice, are summarized in Table 9-1.

Enrollment/Initial visit:

Once a patient is deemed eligible for inclusion, the physician will inform the patient and legal representative (where applicable) about the study. If the patient is interested in participating, the physician will ask the patient (and, if appropriate, the legal representative) to sign the informed consent form. After patients have been enrolled in the study, baseline information is recorded during this initial visit.

Follow-up data collection period:

The follow-up assessments will be completed in the eCRF/EDC system. These assessments do not require the scheduling of any additional visits outside of the standard of care. Due to the observational nature of the study, no specific follow-up visits can be scheduled, and it is unknown when a patient will come for the next visit. Thus, data collection will occur continuously throughout the patient's observation period, i.e., each visit or assessment is to be documented in the eCRF/EDC system. In case a patient is seen by more than one physician (e.g., the patient is monitored by a physician other than the initial treating physician), the initial treating physician should make every effort to collect information on visits that took place (and results that were obtained) outside the treating physician's site. For example, by communicating with the other physician or by having the patient/legal representative obtain a letter with detailed information and results (e.g., ARs, medications given, procedures performed).

End of observation and final safety follow-up:

The final data collection (end of observation) should be after 50 patients have been followed-up for a minimum of 4 years. Final collection of safety data (e.g. AEs) will occur up to 30 days after the last dose of damoctocog alfa pegol within the study period.

Lost to follow-up:

A patient is considered 'lost to follow-up' if no further information can be expected from the patient at a given point in time. If no information had been obtained from a patient within 12 months from the last data collection time point, site personnel are requested to apply due diligence (within the applicable legal limits) to contact patients and ascertain the reason for an absence of information. In case no information can be obtained, the site should confirm that the patient is lost to follow-up and document the end of observation.

Table 9-1: Overview of data collected during the study

	Enrollment/Initial visit	Follow-up visit (including end of observation)
Eligibility Assessment[a]	X	
Date of visit	X	X
Date of informed consent	X	
Demographic data[b] (e.g., date of birth, age, ethnicity, race)	X	
Hemophilia disease history	X	
Hemophilia treatment history (including Damoctocog alfa pegol history, if any)	X	
Medical history and concomitant diseases	X	
Physical examination (weight, height, vital signs)[c]	X	X
Prior and concomitant medications	X	X
Currently prescribed damoctocog alfa pegol regimen	X	X
Damoctocog alfa pegol dose/regimen changes, treatment switches		X (continuous collection)
Damoctocog alfa pegol PK analysis[c]	X	X
AEs, SAEs and ARs (includes systematically collected AEs and AESIs) [d,e]	X (continuous collection)	
FVIII Inhibitor[c]	X	X
Biochemistry[c,f]	X	X
Urinalysis[c,g]	X	X
PEG plasma[c]	X	X
Neurological assessment[c,h]	X	X
Number of bleeding episodes	X	X
Reason(s) for end of observation		X (once, at occurrence)

a: Including confirmation of eligibility criteria or documentation of reason for non-enrollment, where applicable.
b: The availability of demographic variables is likely to vary per country according to legal and ethical regulations. Race will only be collected where legally permitted.
c: If available (i.e., if conducted during routine clinical examination).
d: Events up to 30 days after the last treatment with damoctocog alfa pegol in study period
e: Including duration, treatment, seriousness, and outcome.
f: Sodium, potassium, albumin, creatinine, bilirubin, AST, ALT, GGT, alkaline phosphatase, CRP, urea, eGFR.
g: Urine albumin/creatinine ratio, spot urine dipstick test.
h: Including (for all ages) level of consciousness, cranial nerves, body tone, strength (of the 4 extremities), reflexes, sensory aspects, gait and coordination and fine motor function. In the case of children, evaluation of appearance, language, social interaction. In the case of adults, mental state.
AE: adverse event, AESI: adverse event of special interest, AR: adverse reaction, ALT: alanine aminotransferase, AST: aspartate aminotransferase, CRP: C-reactive protein, eGFR: estimated glomerular filtration rate, FVIII: factor VIII, GGT: gamma-glutamyl transferase, PEG: polyethylene glycol, PK: pharmacokinetics, SAE: serious adverse event.

9.3 Subjects

All PTPs with hemophilia A receiving prophylaxis damoctocog alfa pegol will be eligible to be enrolled into the study. The confirmation of eligibility criteria for patients enrolled or reasons for non-enrollment will be collected in the eCRF/EDC system. The rationale for restricting the study population to patients on prophylaxis treatment is that these patients may

have a higher treatment exposure as compared to 'on-demand' patients. Otherwise, indications according to the local market authorization should be carefully considered.

9.3.1 Inclusion criteria

- Signed informed consent/assent will be obtained before any study-related activities (i.e., any procedure related to the recording of data according to the protocol)
- PTPs with hemophilia A assigned to damoctocog alfa pegol prophylaxis treatment
- Negative FVIII inhibitor test before study entry
- Decision to initiate treatment with commercially available damoctocog alfa pegol has been made by the treating physician before and independently from the decision to include the patient in this study

9.3.2 Exclusion criteria

- Known or suspected contraindications to damoctocog alfa pegol or related products
- Mental incapacity, unwillingness or other barriers precluding adequate understanding or cooperation
- Participation in an investigational program with interventions outside of routine clinical practice

9.4 Variables

The physician collects historical study-relevant data (demographic and clinical characteristics) from medical records if available (or by interviewing the patient at the initial [baseline] visit) and treatment-related data during visits. In this NIS, the visits are not scheduled by the study team (i.e., visits occur at the physicians' discretion and independent of the patients' participation in the study. It is assumed that at most hemophilia treatment centers, patient visit frequency is at least 1-2 times per year). This is a NIS, and the clinical decisions of the physicians must not be affected by study participation. As such, data on many of the secondary endpoints (e.g., PEG plasma, eGFR, ALT) may not be available for all patients. In case an investigator wants to determine PEG plasma levels, e.g., in case of any AE which could be related to PEG accumulation, one or more laboratories will be appointed and kits will be provided to the sites for sampling as per the investigator's discretion. Bayer Consumer Care AG will offer support for the procedure if requested.

Variables to determine the primary endpoint:

Information on (serious) AEs to be collected includes:

- Diagnosis of AE or symptom (if diagnosis unknown)
- Qualification as AE of special interest including hypersensitivity reactions, loss of drug effect, renal impairment, neurocognitive disorders, and inhibitor development
- Start and stop date
- Seriousness
- Reasonable causal relationship to damoctocog alfa pegol treatment
- Action taken
- Event outcome
- Other specific treatment(s) of AE

Information to be documented by the physician regarding inhibitor measurement, if available and collected in routine clinical practice, includes:

- Date of inhibitor measurement
- Inhibitor result (no/yes)
- Titer of inhibitor (Bethesda units)

An AE is any untoward medical occurrence in a patient administered a medicinal product and which does not necessarily have a causal relationship with this treatment. An AE can, therefore, be any unfavorable and unintended sign (e.g., an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to this medicinal product.
An AR is defined as a response to a medicinal product which is noxious and unintended. An AR is any AE judged as having a reasonable suspected causal relationship to damoctocog alfa pegol.
An AE or AR is serious (SAE) if it results in death, is life-threatening, requires in-patient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability or incapacity, is a congenital anomaly or birth defect, or is medically important.
Treatment-emergent adverse events (TEAEs) are defined as any event arising or worsening at or after the first application of damoctocog alfa pegol after study enrollment until 7 days after the last damoctocog alfa pegol infusion during the study.
Further details on management and reporting of AEs are available in the Protocol (Annex 1).

Variables to determine the secondary endpoint:

Laboratory parameters to be documented include (if available and collected in routine clinical practice at the physician's discretion):

- Date of test
- Biochemistry parameters:
    - Sodium, potassium, albumin, creatinine, bilirubin, AST, ALT, gamma-glutamyl transferase (GGT), alkaline phosphatase, C-reactive protein (CRP), urea, eGFR
- Urinalysis parameters:
    - Urine albumin/creatinine ratio and spot urine dipstick test.
- PEG plasma levels

Parameters for neurological assessments to be documented (if available) include the following:

- Date of assessment
- Level of consciousness, cranial nerves, body tone, strength (of the 4 extremities), reflexes, sensory aspects, gait, coordination and fine motor function, mental state
- For children: evaluation of appearance, language, social interaction

9.5 Data sources and measurement

The physician collects historical study-relevant data (demographic and clinical characteristics) from medical records, if available, or else by interviewing the patient. Likewise, the physician collects treatment-related data during visits that take place in routine practice. Patient diaries will be provided to the patients, and they will be trained by the site personnel on how to complete them. Patient diaries will be reviewed for AEs at each visit.

Each patient is identified by a unique central patient identification code, which is only used for study purposes. For the duration of the study and afterwards, only the patient's treating physician or authorized site personnel can identify the patient based on the patient identification code.

In case a patient is seen by more than one physician (e.g., the patient is monitored by a physician other than the initial treating physician), the initial treating physician should make every effort to collect information on any visits (including results) that have taken place outside the treating physician's site, for example by communicating with the other physician or by having the patient/legal representative obtain a letter with detailed information and results, for example of any ARs, medications given, or procedures performed.

9.6 Bias

In general, because of the non-interventional design of this study and limitations inherent to observational studies, findings generated from this study are subject to bias, such as information bias, selection bias, limitations to availability of historical medical data, and differences in treatment or reporting owing to local guidelines. Physicians will be asked to sample consecutive patients whenever possible. This consecutive sampling approach is intended to reduce selection bias.

9.7 Study size

The study aims to observe 50 patients for at least 4 years each, in line with the sample size requested for safety analysis by the European Medicines Agency (EMA). Assuming a dropout rate of approximately 20% (due to lost to follow-up cases or withdrawals), 62 patients were enrolled and enrollment for the study is now closed. The study will continue until 50 patients have reached a minimum follow-up of 4 years. At this time, the study will end for all patients. With an underlying incidence risk of 2% for inhibitor development, there is a 64% chance of observing at least one such event in a sample of 50 patients.

Patients who drop out prior 48 months follow-up will be replaced to ensure that all in all 50 patients have reached a minimum follow-up of 4 years.

9.8 Data transformation

Not applicable.

9.9 Statistical methods

The statistical evaluation will be performed by Cerner Enviza, using the software package SAS release 9.4 (SAS Institute Inc., Cary, NC, United States of America [USA]).

Interim reports will be provided annually to the competent authorities starting 1 year after the first visit of the first patient (FPFV). The final analysis will be performed after the end of the study, which is the date the analytical dataset is completely available.

A detailed description of statistical methods and analyses that are planned for future reports is provided in the statistical analysis plan (SAP) (see Annex 1).

9.9.1 Main summary measures

All variables will be analyzed descriptively with appropriate statistical methods: categorical variables by frequency tables (absolute and relative frequencies) and continuous variables by sample statistics (i.e., mean, standard deviation [SD], minimum [Min], median, quartiles and maximum [Max]).

9.9.2 Main statistical methods

Statistical analyses will be of an explorative and descriptive nature. The study is not aimed to confirm or reject predefined hypotheses; hence no formal hypothesis testing will be performed. All analyses will be performed for the total study population (safety analysis set [SAF]), pharmacokinetics (PK) specific analyses will be performed for the pharmacokinetics analysis set (PKAS). Further details, including specifications of analysis sets and details on analyses of specific variables, are provided in the SAP (see Annex 1).

9.9.3 Missing values

No imputation of missing information will be applied except for partial dates and for weight assessments. Data handling rules are described in the SAP (see Annex 1).

9.9.4 Sensitivity analyses

Not applicable.

9.9.5 Amendments to the statistical analysis plan

The SAP (Annex 1) was updated to version 2.0 on 25 MAY 2023. The following changes were made:

No imputation of missing information will be applied except for missing first date of treatment with damoctocog alfa pegol, partial dates and for weight assessments. If date of first administration of damoctocog alfa pegol in study is missing, then the date will be imputed to signing of informed consent date (SAP section 4.3).

Patient-based shift tables displaying laboratory values at baseline and during follow-up will be provided per each laboratory parameter. For this analysis, baseline (categorized as “normal”, “abnormal” or “missing”) will be compared to one assessment for the follow-up period, based on the worst case: if the patient has at least one “abnormal” value then this will be used; otherwise “normal” value if any, or “missing” if no results were provided during follow-up (SAP section 6.3.2).

Summary tables for urine dipstick tests were removed. Only patient listings will be provided (SAP section 6.3.2).

Patient-based shift tables showing the number and proportion of normal and abnormal item-wise results of the following neurological assessments at baseline versus worst case during follow-up (which is “abnormal” in case of any documentation of “abnormal” during follow-up) (SAP section 6.3.3).

In case of documentation of zero total bleeds, the corresponding kinds of bleeds are also zero. In case of zero spontaneous or trauma bleeds, the number of spontaneous joint bleeds or trauma joint bleeds is also zero (SAP section 6.5.3).

9.10 Quality control

9.10.1 Data quality

Before study start at the sites, all physicians will be sufficiently trained on the background and objectives of the study and on the ethical as well as regulatory obligations. Regular site visits will be performed by trained personnel (e.g., clinical research associates [CRAs]) to monitor data completeness and quality. Details are specified in the quality review plan (QRP) (see Annex 1). All observations will be recorded in a standardized eCRF. The eCRF is part of the EDC system which allows documentation of all outcome variables and covariates by all participating sites in a standardized way. After data entry, missing or implausible data will be

queried, and the data will be validated. A check for multiple documented patients will be performed. Detailed information on checks for completeness, accuracy, plausibility, and validity are given in the data management plan (DMP). The DMP will specify measures for handling of missing data and permissible clarifications, (see Annex 1). Medical review of the data will be performed according to the Medical Review Plan (MRP), (see Annex 1).

9.10.2 Quality review

All sites (which have enrolled at least one patient) will be visited regularly. Each site will be selected for a first on-site visit approximately 8 weeks after FPFV.
Further visits will follow on an annual basis. Due to the low number of patients in the study all patients will be reviewed, and a complete source data verification will be performed. Additional quality review on-site visits may be scheduled (e.g., due to findings from remote checks or according to other criteria associated with the performance of the site). On-site data reviews must be conducted by adequately trained reviewers. The purpose is to review the documented data for completeness and plausibility, adherence to the study protocol and verification with source documents. Detailed measures for quality reviews will be described in the QRP (see Annex 1).

9.10.3 Storage of records and archiving

Bayer Consumer Care AG will ensure that all relevant documents for this study will be stored after the end or discontinuation of the study for at least 25 years. Any data, as well as programs from statistical programming performed to generate results, will be stored within the programming system for at least 25 years. Other instructions for storage of medical records will remain unaffected. The physicians participating in the study are required to archive documents at their sites according to local requirements, considering possible audits and inspections from Bayer Consumer Care AG and/or local authorities. It is recommended to store documents for a retention period of at least 25 years at the study sites.

10. Results

Variables were analyzed as described in Section 9.9. As the study is still active, regular data cleaning activities are ongoing and will continue until database lock at the end of the study. Follow-up visits occur during routine practice. In this NIS, the exact referral dates for those visits are not defined in the study protocol. After the initial visit, data collection will continue for a minimum of 48 months.

All results are presented in the statistical output tables, figures, listings (TFL) (see Annex 1).

10.1 Participants

At the time of the second interim analysis, a total of 62 patients were enrolled in the HA-SAFE study. All 62 patients were included in the SAF. It should be noted that a negative FVIII inhibitor test was required for inclusion in the study.

In the PKAS, 25 patients were included, while 37 patients were excluded since they did not have any documented PK values yet (TFL, Table 14.1.1 and Table 14.1.2).

At the time of the second interim analysis, the median number of days in the study for all patients (n=62) was 68.5 days. Note that one patient had discontinued the study due to a switch to on-demand therapy with damoctocog alfa pegol (TFL, Table 14.1.3 and Table 14.1.4).

The median observation period for patients with at least 1 follow-up visit (n=35) was 213 days (i.e., approximately 7 months). Further details on types of visits and number of follow-up visits are provided in Tables 14.1.5-14.1.7.

10.2 Descriptive data

Demographic characteristics of the patients in the SAF are presented in Table 10-1.

Table 10-1: Demographics – SAF

Parameter	SAF N=62
Country, n (%)	
Germany	35 (56.45%)
Greece	7 (11.29%)
Italy	6 (9.68%)
Spain	11 (17.74%)
Austria	3 (4.84%)
Sex, n (%)	
Male	62 (100.00%)
Female	0 (0.00%)
Race, n (%)	
White	54 (87.10%)
Black or African American	0 (0.00%)
Asian	3 (4.84%)
American Indian or Alaska native	0 (0.00%)
Native Hawaiian or other Pacific islander	0 (0.00%)
Not reported	5 (8.06%)
Ethnicity, n (%)	
Not Hispanic or Latino	58 (93.55%)
Hispanic or Latino	3 (4.84%)
Not reported	1 (1.61%)
Blood type, n (%)	
A	17 (27.42%)
B	3 (4.84%)
AB	2 (3.23%)
O	13 (20.97%)
Unknown	27 (43.55%)
Age [a] (years)	
N	62
Mean (SD)	37.8 (13.94)
Median	38.0
Q1, Q3	28.0, 49.0
Min, Max	12, 69
Age[a] (categories)	
<12 years	0 (0.00%)
≥12 to <18 years	6 (9.68%)
≥18 to <65 years	54 (87.10%)
≥65 years	2 (3.23%)

a: Age at time of signing informed consent.
Max: maximum, Min: minimum, N: number of patients in analysis set, n: number of patients with observations, Q1/3: first/third quartile, SAF: safety analysis set, SD: standard deviation.
Source: TFL, Table 14.2.1.

All patients in the SAF were male, the vast majority were White (87.10%) and not Hispanic or Latino (93.55%). Most patients were from Germany (56.45%), followed by Spain (17.74%), Greece (11.29%), Italy (9.68%), and Austria (4.84%). The mean ± SD age was 37.8 ± 13.94years (ranging from 12 to 69 years), with most patients being ≥18 to <65 years (54 patients, 87.10%), 6 patients (9.98%) being adolescents (≥12 to <18 years), and 2 patients being ≥65 years.

Vital signs at baseline are provided in TFL, Table 14.2.2.

Out of the 62 patients analyzed in this report, 56 patients were diagnosed with severe and 6 patients with moderate hemophilia A and 35 patients were carrying gene mutations.

Looking at the type of gene mutation, 12 patients carried an Intron 22 inversion, 13 patients carried a missense mutation, 2 patients carried a nonsense mutation, 5 patients carried a small deletion, 2 patients carried a large deletion, and 1 patient carried a splice site mutation. For 19 patients these data were not available and for 8 patients the type of gene mutation was 'other'. Family history of inhibitors was reported for 3 patients, while 44 patients had no family history of inhibitors, and for 15 patients this information was unknown. Regarding patients' own history, 13 patients presented with history of inhibitors, while 49 patients had no history of inhibitors.

At any time before enrollment, on-demand treatment was reported for 29 patients (46.77%), while 33 patients (53.23%) did not have previous on-demand treatment. All but 5 patients (57 patients, 91.94%) were on prophylaxis with damoctocog alfa pegol before enrollment in the study, with a median exposure time of 12.0 months (Q1, Q3: 10.0, 24.0) (TFL, Table 14.2.3, Table 14.2.5).

A summary of bleeds within 12 months prior to enrollment is provided in TFL, Table 14.2.4, and a listing of most recent hemophilia treatment prior to enrollment is in Listing 14.2.6.

Overall, 21 patients (33.87%) had at least one prior disease (not ongoing at study entry) (see TFL, Table 14.2.7.1). Concomitant diseases were reported for 41 patients (66.13%), with the most common being chronic arthropathy (20 patients, 32.26%), followed by chronic pain (12 patients, 19.35%), human immunodeficiency virus test positive (7 patients, 11.29%), Hepatitis C virus test positive (3 patients,14. 4.84%), liver disease (1 patient, 1.61 %) and neurological disorder (1 patient, 1.61%). In addition, 23 patients (37.10%) were listed as other finding (diagnosis, disease or surgery) (TFL, Table 14.2.7.2).

The number of patients with prior disease and concomitant disease by SOC and preferred term (PT) is documented in TFL Tables 14.2.8.1 and 14.2.8.2 respectively.

Overall, 36 patients (58.06%) had at least one concomitant medication (TFL, Table 14.3.1).

10.3 Outcome data

Data on demographics and baseline characteristics are provided in Section 10.2. Results on primary and secondary outcome variables are presented in Section 10.4.

10.4 Main results

10.4.1 Primary Endpoints (Adverse events / adverse reactions)

An overview of AEs is shown in Table 10-2.

Table 10-2: Summary of adverse events – SAF

Number (%) of patients with the specified AE	N=62
Any TEAE	22 (35.48%)
Any AR	1 (1.61%)
Any TEAESI	1 (1.61%)
Unrelated	0 (0.00%)
Related	1 (1.61%)
Hypersensitivity Reaction	0 (0.00%)
Loss of Drug Effect	1 (1.61%)
Inhibitor Development against Factor VIII	1 (1.61%)
Renal Impairment	0 (0.00%)
Neurocognitive Disorder	0 (0.00%)
Any TESAE	8 (12.90%)
Any serious AR	1 (1.61%)
Any TESAESI	1 (1.61%)
Unrelated	0 (0.00%)
Related	1 (1.61%)
Hypersensitivity Reaction	0 (0.00%)
Loss of Drug Effect	1 (1.61%)
Inhibitor Development against Factor VIII	1 (1.61%)
Renal Impairment	0 (0.00%)
Neurocognitive Disorder	0 (0.00%)
Maximum intensity of TEAE	
Severe	4 (6.45%)
Moderate	6 (9.68%)
Mild	11 (17.74%)
Missing	1 (1.61%)

TEAEs/TESAEs are defined as any event arising or worsening at or after the first application of damoctocog alfa pegol after study enrollment until 7 days after the last damoctocog alfa pegol infusion during the study.
TEAESIs/TESAESIs are those events qualified as hypersensitivity reaction, loss of drug effect, inhibitor development, renal impairment, or neurocognitive disorder.
Post-treatment AEs are AEs occurring after 7 days and up to 30 days after last study drug intake.
AE: adverse event, AR: adverse reaction, N: number of patients in analysis set, SAF: safety analysis set, TEAE: treatment-emergent adverse event, TEAESI: treatment-emergent adverse event of special interest, TESAE: treatment-emergent serious adverse event, TESAESI: treatment-emergent serious adverse event of special interest.
Source: TFL, Table 14.4.1.

Among the 62 patients in the SAF, 22 patients (35.48%) experienced a total of 43 TEAEs (TFL, Table 14.4.5). A total of 8 patients (12.90%) experienced a treatment-emergent serious adverse event (TESAE), one of which was reported as drug-related (AR). One of the reported events was a treatment-emergent adverse event of special interest (TEAESI) involving loss of drug effect and low titer inhibitor development against factor VIII, which was classified as serious (TESAE). There were no deaths.

On review of patients with TEAEs with maximum intensity, overall, 6 patients had TEAEs of moderate intensity (9.68%), 4 patients had a TEAE of severe intensity (6.45%), and 11 patients had a TEAE of mild intensity (17.74%), in one patient (1.6%) the intensity was not

reported (TFL, Tables 14.4.1-14.4.5). Further, no TEAEs leading to discontinuation of damoctocog alfa pegol were reported (TFL, Table 14.4.3.2).

TEAEs by Medical Dictionary for Regulatory Activities (MedDRA) SOC and PT are shown in Table 10-3.

Table 10-3: Number of patients with any TEAEs by primary SOC and PT – SAF

	Incidence
Number (%) of patients with at least one TEAE	22 (35.48%)
Gastrointestinal disorders	1 (1.61%)
- Constipation	1 (1.61%)
General disorders and administration site conditions	5 (8.06%)
- Pain	1 (1.61%)
- Pyrexia	2 (3.23%)
- Swelling	1 (1.61%)
- Vaccination site bruising	1 (1.61%)
Infections and infestations	4 (6.45%)
- COVID-19	2 (3.23%)
- Gastrointestinal infection	1 (1.61%)
- Herpes simplex	1 (1.61%)
Injury, poisoning and procedural complications	5 (8.06%)
- Epicondylitis	1 (1.61%)
- Face injury	1 (1.61%)
- Fall	1 (1.61%)
- Injury	1 (1.61%)
- Joint injury	1 (1.61%)
- Ligament sprain	1 (1.61%)
Musculoskeletal and connective tissue disorders	5 (8.06%)
- Arthralgia	3 (4.84%)
- Haemarthrosis	1 (1.61%)
- Intervertebral disc protrusion	1 (1.61%)
- Joint range of motion decreased	1 (1.61%)
- Osteopenia	1 (1.61%)
- Trigger finger	1 (1.61%)
Not coded	6 (9.68%)
- Dislocated infractionfracture of condylus femoris	1 (1.61%)
- Dislocated infractionfracture of tibiaplateau	1 (1.61%)
- Gastrointestinal infection with diarrhea	1 (1.61%)
- Joint bleed left ankle left	1 (1.61%)
- Joint bleed elbow	1 (1.61%)
- Joint bleed knee	1 (1.61%)
- Low titer factor viii inhibitor	1 (1.61%)
- Renal colic	1 (1.61%)
Nervous system disorders	1 (1.61%)
- Headache	1 (1.61%)
Renal and urinary disorders	2 (3.23%)
- Haematuria	1 (1.61%)
- Renal infarct	1 (1.61%)
Surgical and medical procedures	5 (8.06%)
- Hernia repair	1 (1.61%)
- Orchidectomy	1 (1.61%)
- Removal of internal fixation	1 (1.61%)
- Tooth extraction	1 (1.61%)
- Transurethral prostatectomy	1 (1.61%)
Vascular disorders	2 (3.23%)
- Haematoma	2 (3.23%)

AEs are sorted in alphabetical order by primary SOC and PT.
A patient is counted only once within each PT of any primary SOC.
For interim reports, calculation of therapy duration is based on a conservative approach, i.e., up to last

documented visit.
a: If therapy duration is zero, EAIR is not calculated.
AE: adverse event, CI: confidence interval, EAIR: exposure adjusted incidence rate, NA: not applicable, PT: preferred term, SAF: safety analysis set, SOC: system organ class.
Source: TFL, Table 14.4.2.1.

The most common TEAEs were reported in the SOCs General disorders and administration site conditions, Injury, poisoning and procedural complications, and Musculoskeletal and connective tissue disorders, Surgical and medical procedures (5 patients, 8.06% each), followed by Infections and infestations (4 patients, 6.45%), Vascular disorders and Renal and urinary disorders (2 patients, 3.23% each), Gastrointestinal disorders, and Nervous system disorders (1 patient, 1.61% each). For 6 patients (9.68%), the TEAEs were not coded at the DLP of this report. PTs that occurred in more than 1 patient were arthralgia (3 patients, 4.84%), COVID-19, haematoma, and pyrexia (2 patients, 3.23% each).

Overall, 9 patients (14.52%) experienced TEAEs leading to a change of treatment regimen (TFL, Table 14.4.3.3). With the exception of arthralgia (reported in 3 patients), all of the events were reported once only. None of the TEAEs was reported with a frequency of ≥5%.

A total number of 43 TEAEs were documented (TFL, Table 14.4.5). Of all AEs, the majority (27 events) were of mild intensity, 11 were moderate, and 4 were severe. Information on severity was missing for 1 patient. Of the 4 severe TEAEs, 2 were recovered/resolved without dose increase, one resolved with a dose increase and one was not resolved. The majority of the reported TEAEs (38 TEAEs) were recovered/resolved or recovering/resolving with 15 requiring a dose increase, and one requiring a dose reduction. Three TEAEs were not resolved and 2 had an unknown outcome (TFL, Listing 14.4.6).

All TESAEs were reported in only one patient each, with the PTs haematoma, haematuria, hernia repair, low titer factor VIII inhibitor, orchidectomy, removal of internal fixation, renal infarct, and transurethral prostatectomy (TFL,Table 14.4.2.3).

One TEAESI (classified as an AR) was noted for one patient (low titer factor VIII inhibitor of moderate intensity) which recovered without discontinuation of damoctocog alfa pegol (TFL, Listing 14.4.7.1 and Listing 14.4.8). The following additional details of this patient were entered into the database or received directly from the study site by Bayer Pharmacovigilance. Some of the data are not included in the TFL and are subject to a reconciliation / clarification between the clinical and safety databases:

- Patient age at enrollment: 46 years.
- Patient was pre-treated with damoctocog alfa pegol for 6 months before the study. Previous measurements of FVIII inhibitor annually since 2006 were always negative. The last measurement for antibodies against FVIII before inclusion was on 03 MAY 2022 and was negative.
- Start date of the SAE: 09 NOV 2022 (date of enrollment); Patient presented themselves to outpatient clinic for routine control after switching to damoctocog alfa pegol prophylaxis. There were no bleeding events reported. FVIII trough level was 0.5% 4 days after last administration of 3000 IU damoctocog alfa pegol. FVIII inhibitor level was found as 2.9 Bethesda Units (BU) (assay method: Bethesda); FVIII post-administration and recovery levels were not provided. On 14 NOV 2022 FVIII inhibitor level decreased to 1.8 BU.
- On 14 NOV 2022 a FVIII epitope mapping was performed and confirmed a specific antibody against FVIII (isotype IgG, subclass IgG 4 with binding to HC, A1 and A2 domains), no binding to PEG.
- 07 MAR 2023: The patient continued therapy with damoctocog alfa pegol. On 07 MAR 2023, the FVIII level was 17% 42 hours after the last substitution. Inhibitors

were no longer detected. The event was considered resolved. Follow up of the case is ongoing.

No TEAE resulted in death (TFL, Listing 14.4.7.2).

A listing of all TEAEs leading to change of treatment regimen is documented in TFL Listing 14.4.7.3. Ten were mild, 5 were moderate and one was severe. All TEAEs leading to change of treatment regimen were recovered/resolved, with 15/16 requiring a dose increase while one was resolved with a dose decrease. The events leading to the increase in the dose were mostly attributable to trauma (e.g., fall, ligament sprain), surgical interventions or typical manifestations of hemophilia patients (e.g., bleed, haemarthrosis). All of these TEAEs were assessed as unrelated to damoctocog alfa pegol. No TEAEs resulting in discontinuation of treatment were reported (TFL, Listing 14.4.7.4).

Inhibitor measurements were available for 25/62 patients, all test results were negative; 5 patients had 2 negative tests, 2 patients had 3 negative tests, and one patient had 5 negative tests (TFL, Table 14.5.1 and Listing 14.5.2). It should be noted that for technical reasons the test details of the low titer inhibitor reported as TEAESI for one patient at study entry were not entered into the database (see above for further details on the TEAESI).

10.4.2 Secondary endpoints

No AR was reported related to any of the secondary endpoints referring to the SOCs Nervous system disorders, Psychiatric disorders, Renal and urinary disorders, and Hepatobiliary disorders. Data regarding laboratory assessments are unclean, with some of the values being queried, and are therefore to be interpreted with caution.

Neurological function

No ARs from the SOCs Nervous system disorders and Psychiatric disorders were reported. Abnormal gait was observed for one patient at baseline but was normal at follow-up (TFL, Table 14.4.2.5 and Table 14.7.1). One additional patient was found with abnormal gait at baseline, however no follow-up data were available, so these data were not included in the TFL and no AE was reported for this patient.

Renal function

No ARs from the SOC Renal and urinary disorders were reported. In the majority of patients with collected laboratory data no abnormal levels were observed for urea levels, creatinine, eGFR, potassium, and sodium at baseline and follow-up. In one patient eGFR of 45 ml/min was reported at baseline but was not associated with an AE. No follow-up data are available for this patient (TFL, Table 14.4.2.5,Table 14.6.1 and Table 14.6.2). Details are shown in Table 10-4.

Hepatic function

No ARs from the SOC Hepatobiliary disorders were reported. In the majority of patients with collected laboratory data no abnormal values were observed for albumin, alkaline phosphatase, ALT, AST, bilirubin, and GGT at baseline and follow-up. In a small number of patients some laboratory values outside of the normal range were reported on single occasions, none which were reported as TEAEs. One patient, who had normal liver parameters at baseline and discontinued from the study, was found with elevated liver transaminases later on (ALT of 150 U/L and AST 64 U/L). After the DLP it was clarified that bilirubin remained within the normal range and that the elevated liver enzymes were assessed as unrelated to damoctocog alfa pegol. Data cleaning efforts are ongoing (TFL, Table 14.4.2.5, Table 14.6.1 and Table 14.6.2). Details are shown in Table 10-4.

PEG plasma levels

No assessment of PEG plasma levels has been done so far.

Table 10-4: Summary statistics and change from baseline by visit for biochemistry lab parameters – SAF

Parameter	N	n	Mean (SD)	Median	Q1, Q3	Min, Max
Albumin (g/L)						
Baseline	62	18	4.82 (0.749)	4.58	4.50, 4.86	4.1, 7.5
Follow-up window 1	22	7	4.77 (0.457)	4.79	4.40, 5.07	4.1, 5.5
Follow-up window 2	14	4	4.40 (0.245)	4.45	4.20, 4.60	4.1, 4.6
Alkaline Phosphatase (U/L)						
Baseline	62	29	101.9 (68.81)	83.0	63.0, 104.0	49, 324
Follow-up window 1	22	11	98.1 (65.47)	74.0	57.0, 115.0	42, 279
Follow-up window 2	14	6	75.8 (23.71)	78.5	57.0, 89.0	44, 108
Follow-up window 3	1	0				
ALT (U/L)						
Baseline	62	36	29.3 (23.54)	24.0	15.5, 34.5	6, 132
Follow-up window 1	22	11	26.7 (12.52)	24.0	20.0, 30.0	12, 56
Follow-up window 2	14	9	37.6 (43.51)	23.0	16.0, 36.0	13, 150

Parameter	N	n	Mean (SD)	Median	Q1, Q3	Min, Max
Follow-up window 3	1	0				
AST (U/L)						
Baseline	62	35	27.0 (16.90)	23.0	21.0, 29.0	13, 111
Follow-up window 1	22	11	25.0 (9.56)	23.0	14.0, 32.0	13, 40
Follow-up window 2	14	9	26.7 (15.44)	21.0	18.0, 29.0	15, 64
Follow-up window 3	1	0				
Bilirubin (mg/dL)						
Baseline	62	27	0.65 (0.244)	0.60	0.50, 0.79	0.3, 1.6
Follow-up window 1	22	0				
Follow-up window 2	14	0				
Follow-up window 3	1	0				
Creatinine (mg/dL)						
Baseline	62	36	0.86 (0.186)	0.86	0.75, 0.97	0.4, 1.5
Follow-up window 1	22	11	0.89 (0.169)	0.84	0.80, 1.02	0.6, 1.2
Follow-up window 2	14	8	0.87 (0.118)	0.82	0.81, 0.97	0.7, 1.0
Follow-up window 3	1	0				
CRP (mg/L)						
Baseline	62	24	0.186 (0.2122)	0.100	0.035, 0.325	0.00, 0.70
Follow-up window 1	22	10	0.210 (0.1573)	0.170	0.070, 0.339	0.06, 0.54
Follow-up window 2	14	6	0.070 (0.0473)	0.055	0.040, 0.080	0.03, 0.16
Follow-up window 3	1	0				
eGFR (mL/min)						
Baseline	62	34	107.3 (23.45)	107.0	90.0, 119.0	45, 172
Follow-up window 1	22	11	97.7 (16.87)	90.0	89.0, 113.0	75, 135
Follow-up window 2	14	8	101.7 (17.68)	100.0	90.0, 115.3	75, 128
Follow-up window 3	1	0				
GGT (U/L)						
Baseline	62	33	22.5 (11.86)	19.0	12.0, 30.0	7, 60
Follow-up window 1	22	11	27.5 (9.73)	26.0	19.0, 32.0	15, 50
Follow-up window 2	14	9	26.0 (10.91)	28.0	16.0, 33.0	11, 41
Follow-up window 3	1	0				
Potassium (mmol/L)						
Baseline	62	19	4.24 (0.271)	4.30	4.03, 4.40	3.5, 4.6
Follow-up window 1	22	5	4.10 (0.374)	4.10	3.90, 4.10	3.7, 4.7
Follow-up window 2	14	4	4.25 (0.173)	4.30	4.15, 4.35	4.0, 4.4
Follow-up window 3	1	0				
Sodium (mmol/L)						
Baseline	62	19	139.9 (1.68)	140.0	139.0, 141.0	137, 144
Follow-up window 1	22	6	140.5 (2.88)	140.5	140.0, 141.0	136, 145
Follow-up window 2	14	4	139.8 (1.89)	140.5	138.5, 141.0	137, 141
Follow-up window 3	1	0				
Urea (mg/dL)						
Baseline	62	28	28.6 (10.46)	30.0	22.5, 33.5	10, 53
Follow-up window 1	22	10	31.9 (4.88)	33.0	31.0, 35.0	21, 38
Follow-up window 2	14	6	25.2 (7.00)	25.0	20.0, 29.0	16, 36
Follow-up window 3	1	0				

The follow-up window is defined sorting follow-ups into a predefined visit schedule of 180-day intervals (±90 days) starting from baseline. In case of multiple assessments within one 180-day window, the assessment with the lowest date distance to the optimal date (midpoint of respective window) is selected. In case of multiple assessments with equal distance to the optimal date, the earlier assessment is chosen. Information collected after the initial visit up to <90 days later are not assigned to any follow-up window and not included in summary statistics by window.

ALT: alanine aminotransferase, AST: aspartate aminotransferase, CRP: C-reactive protein, eGFR: estimated glomerular filtration rate, GGT: gamma-glutamyl transferase, N: number of patients in analysis set, n: number of patients with observation, Q1/3: first/third quartile, SAF: safety analysis set, SD: standard deviation, U: unit.

Source: TFL, Table 14.6.1.

In summary, no laboratory abnormalities were observed at baseline or at follow-up in the majority of the patients with the reported laboratory values. In a small number of patients some

laboratory values outside of the normal range were reported on single occasions. None of the laboratory values outside the normal range was reported as a TEAE. Data is unclean, some of the values are being queried. A shift table for laboratory abnormalities is shown in TFL, Table 14.6.2, and listings of all laboratory measurements and urine dipstick tests are provided in Listing 14.6.3 and Listing 14.6.4, respectively.

10.5 Other analyses

10.5.1 Bleeding events

A total of 62 bleeding events were reported at the time of the second interim analysis in 21 patients. of which 18 were spontaneous (9 classified as mild, 6 moderate, and 3 severe), and 44 trauma bleeds (30 classified as moderate, 12 mild, and 2 severe), respectively.

The majority of the bleeds were joint bleeds (37 bleeds), 8 were muscle bleeds, 12 were skin/mucosa bleeds, 4 were internal bleeds and 1 was an undefined bleed. Patients had a median (Q1, Q3) number of 2.0 (1.0, 3.0) bleeds (TFL, Tables 14.11.1, 14.11.2, and Listing 14.11.3).

Three bleeds were considered as SAEs, two of them were trauma bleeds and one was a spontaneous bleed. All were recovered following damoctocog alfa pegol dose increase (TFL, Listing 14.4.6 and Listing 14.11.3).

10.5.2 Drug exposure

The mean ± SD total dose per infusion was 3241.9 ± 1023.26 (median 3000) international units (IU) in all 62 patients. Based on available data for 57 patients the mean ± SD first dose per infusion in the study was 40.51 ± 12.31 IU/kg (median: 42.86 IU/kg), and the first weekly dose was 6092.6 ± 2196.41 IU (n=61, median: 5600 IU) (TFL, Table 14.8.1). The mean ± SD total annual dose was 3568.06 ± 1583.22 IU/kg (n=56, median: 3691.45 IU/kg). The mean ± SD total dose was 2526.33 ± 2036.33 IU/kg (n=56, median: 1973.95 IU/kg) for prophylaxis prescriptions. Doses for surgery were only available for one patient. For serious bleeds, dose increases were reported, however actual doses are unknown (TFL, Tables 14.8.2.1-14.8.2.4).

The most common first prescribed treatment regimen was every 5 days (22 patients, 35.5%). Twice weekly was reported in 14 cases (22.6%), whereas every 7 days was reported in 3 cases (4.8%). Other dosing regimen was selected in 23 patients (37.1%). This distribution was similar for the last prescribed treatment regimen, with few shifts observed (TFL, Table 14.8.4). Further details on prescriptions are available in TFL, Table 14.8.3. There were 104 prescription changes, with the most common reason listed as clinical decision (n=26), followed by adverse event (n=17), and increase in bleeding frequency (n=3). In addition, 56 patients had their prescription changed for other reasons (TFL, Table 14.8.5). A listing of general damoctocog prescriptions prior to and during observation period is provided in TFL Listing 14.8.6.

PK assessments

PK assessments were performed for 25 patients since the first damoctocog alfa pegol treatment in the study. Of these, 14 patients had 1 PK assessment performed, 9 had 2 PK assessments and 2 had 3 PK assessments (TFL, Table 14.9.1, Listing 14.9.2).

Vital signs

Summary statistics and change from baseline by follow-up window for vital signs including weight, height, body mass index (BMI), systolic blood pressure, diastolic blood pressure and

heart rate are presented in TFL, Table 14.10.1. Shift Table for BMI categories is presented in Table 14.10.2.

10.6 Adverse events/adverse reactions

TEAEs, TESAEs, and ARs are presented in Section 10.4.1.

11. Discussion

11.1 Key results

This is the second interim report of a post-authorization safety study (PASS) focusing to characterize the long-term safety of real-world treatment with damoctocog alfa pegol in PTPs with hemophilia A with an observation period of at least 4 years for each patient.

At the time of the cut-off (DLP as of 5 MAY 2023) of this report approximately two years after FPFV (14 MAY 2021), a total of 62 patients were enrolled, all of which have been included in the SAF with a median observation period of 213 days in the study. The vast majority (57 patients, 91.94%) were on prophylaxis with damoctocog alfa pegol for a median of 12 months before enrollment in the study.

All 62 patients were treated with damoctocog alfa pegol as per EU product labelling with the most common treatment regimen being every 5 days (35.5%), twice weekly was reported in 14 cases (22.6%), whereas every 7 days was reported in 3 cases (4.8%).

All patients were male, the vast majority being White (87.10%) and coming from various European countries including Germany (56.45%), Spain (17.74%), Greece (11.29%), Italy (9.68%) and Austria (4.84%). The mean ± SD age was 37.8 ± 13.94 years. Out of the 62 patients analyzed in this report, 56 patients were diagnosed with severe hemophilia A and 6 patients with moderate hemophilia A. Over half of the patients carried associated genetic mutations.

Among the 62 patients in the SAF, 22 patients (35.48%) experienced a total of 43 TEAEs. The majority of the patients had TEAE of mild or moderate intensity (11 mild (17.74%) and 6 moderate (9.68%), respectively). The majority of the reported TEAEs (38 / 43 TEAEs) were recovered/resolved or recovering/resolving. Overall, 9 patients (14.52%) experienced 16 TEAEs leading to a change of treatment regimen all unrelated to damoctocog alfa pegol (15 TEAEs required a dose increase (due to traumatic events, surgery or bleeding evnts), and one required a dose decrease because of TEAE of pain. Further, no TEAEs leading to discontinuation of damoctocog alfa pegol were reported.

A total of 8 patients (12.90%) experienced TESAEs of which one event was reported as drug-related (AR); This event was documented as TEAESI involving development of low titer factor VIII inhibitors and was assessed as loss of drug effect by the site. The patient recovered without discontinuation of prophylactic treatment with damoctocog alfa pegol and remained in the study.

There were no deaths.

No AR was reported related to any of the secondary endpoints referring to the SOCs Nervous system disorders, Psychiatric disorders, Renal and urinary disorders, and Hepatobiliary disorders. Data regarding laboratory assessments is unclean, with some of the values being queried and are therefore to be interpreted with caution. In the majority of the patients with the reported laboratory values no laboratory abnormalities were found. In a small number of patients isolated laboratory values outside of the normal range were reported on single

occasions, including at baseline. None of the laboratory values outside the normal range was reported as a TEAE.

No safety concern has been identified based on the available data.

11.2 Limitations

In general, due to the NIS design, the information to be collected is limited to and depending on the visits/assessments occurring in routine clinical practice. Therefore, hepatic and renal function as well as neurological assessments are depending on the physician's judgment. Nevertheless, any clinically relevant change in organ functions or development of new symptoms shall be documented as AE and will trigger a lab assessment in routine clinical practice. Limited availability of treatment data and underreporting of safety outcomes may be a limitation if a patient leaves the study and/or cannot be followed-up adequately (e.g., withdrawal of consent or loss to follow-up).

11.3 Interpretation

Not applicable

11.4 Generalizability

Not applicable

11.5 Other information

Not applicable

11.6 Conclusion

At the time of the second interim analysis approximately 2 years after study start, 22 patients had experienced any TEAE. A total of 8 patients experienced a TESAE. One TEAESI (classified as an AR) was noted for one patient (low titer factor VIII inhibitor of moderate intensity) which recovered without discontinuation of damoctocog alfa pegol. The majority of the reported TEAEs were of mild or moderate intensity and were recovered/resolved or recovering/resolving at the time of this report. No TEAEs leading to discontinuation of damoctocog alfa pegol were reported and no indication of renal impairment or neurocognitive disorder was observed. Based on these results obtained from the HA-SAFE study, it can be concluded that damoctocog alfa pegol treatment is safe, thus confirming a positive benefit-risk ratio.

12. References

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