Post Authorization Safety Study (PASS) 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
Protocol version and date	v 1.0, 13 JAN 2020
IMPACT study number	20904
Study type / Study phase	Observational, post-approval ☒ PASS Joint PASS: ☐YES ☒ NO
EU PAS register number	Study not yet registered
Active substance	ATC code: B02BD02/Hematological/Damoctocog alfa pegol
Medicinal 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
Study Initiator and Funder	Bayer Consumer Care AG, Basel, Switzerland
Research question and objectives	The aim of this study is to characterize in a real-world setting the long-term safety of damoctocog alfa pegol drug usage. 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 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 is to monitor the clinical effects of long-term exposure of prophylaxis damoctocog alfa pegol in

	patients with hemophilia A, including assessments of kidney and liver function parameters, neurological function and patients' PEG plasma levels.
Country(-ies) of study	The study will be conducted in Europe, countries are not yet identified. Potential countries are Austria Belgium/Luxemburg, Finland, Germany, Greece, Italy, Netherlands, Portugal, Scandinavia (Denmark, Norway, and Sweden), Slovenia, Spain, and Switzerland. The study may also be conducted in other countries not currently listed.
Author	PPD PPD

Marketing authorization holder

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

The study will be conducted in compliance with the protocol
and any applicable regulatory requirements.

Throughout this document, symbols indicating proprietary names (®, TM) may not be displayed. Hence, the appearance of product names without these symbols does not imply that these names are not protected.

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List of Tables

2. List of abbreviations

AE	Adverse Event
ALT	Alanine Aminotransferase
AR	Adverse Reaction
AST	Aspartate Aminotransferase
BDD-rFVIII	B-domain-deleted recombinant factor VIII
CFR	Code of Federal Regulations
CRA	Clinical Research Associate
CRO	Contract Research Organization
CRP	C-Reactive Protein
DMP	Data Management Plan
EDC	Electronic Data Capture
EFPIA	European Federation of Pharmaceutical Industries and Associations
eCRF	Electronic Case Report Form
eGFR	Estimated Glomerular Filtration Rate
EMA	European Medicine Agency
ENCePP	European Network of Centers in Pharmacoepidemiology and Pharmacovigilance
EU	European Union
FDA	US Food and Drug Administration
FVIII	Factor VIII
GGT	Gamma-Glutamyl Transferase
GPP	Good Publication Practice
GVP	Good Pharmacovigilance Practice
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IRB	Institutional Review Board
IU	International Units
MAH	Marketing Authorization Holder
MedDRA	Medical Dictionary for Regulatory Activities
MRP	Medical Review Plan
PAS	Post-Authorization Study
PASS	Post-Authorization Safety Study
PRAC	Pharmacovigilance Risk Assessment Committee
pCRF	Paper Case Report Form
PEG	Polyethylene Glycol
PK	Pharmacokinetic
PT	Preferred Term
PTPs	Previously Treated Patients
QPPV	Qualified Person Responsible For Pharmacovigilance
QRP	Quality Review Plan
rFVIII	Recombinant factor VIII

SAE	Serious Adverse Event
SAF	Safety Analysis Set
SAP	Statistical Analysis Plan
SOC	System Organ Class
STROBE	Strengthening the Reporting of Observational Studies in Epidemiology

3. Responsible parties

3.1 Study initiator and funder

Role:	Study Conduct Responsible
Name:	PPD
E-mail:	PPD
Role:	Qualified Person responsible for Pharmacovigilance (QPPV)
Name:	PPD
Role:	MAH contact person (Regulatory Affairs)
Name:	PPD
Role:	Study Safety Lead
Name:	PPD
Role:	Study Medical Expert
Name:	PPD
Role:	Study Statistician
Name:	PPD
Role:	Study Data Manager
Name:	PPD
Role:	Study Epidemiologist
Name:	PPD
Role:	Regulatory Affairs responsible
Name:	PPD
Role:	Real-World Evidence Strategy Lead
Name:	PPD

Contact details of the responsible parties at Bayer AG are available upon request. Signatures of the responsible parties are collected in Annex 5.

3.2 Collaborators/Committees

Contact details on the coordinating and/or principal investigators, co-investigators and other site personnel for each country and site participating in the study are listed in a stand-alone document (see Table 3) which is available upon request.

Administrative changes of responsible persons and/or the composition of the committees will be documented by updating the respective lists, but do not require formal protocol amendments.

4. 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
Protocol version and date	v 0.5, 26 AUG 2019
IMPACT study number	20904
Study type / Study phase	Observational, post-approval ☒ PASS Joint PASS: ☐YES ☒ NO
Author	PPD
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. Damoctocog alfa pegol is approved for prophylaxis and treatment of bleeds in previously treated patients (PTPs) with hemophilia A aged ≥12 years, with a two 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. These results will elucidate the safety profile of real-world prophylaxis with damoctocog alfa pegol. 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. However, outside of the clinical study, there are currently little real-world safety data on the use of the product.

Research question and objectives	The aim of this study is to characterize in a real-world setting the long-term safety of damoctocog alfa pegol drug usage. Primary objective 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 PEG accumulation (hypersensitivity reactions, loss of drug effect, renal impairment, neurocognitive disorders, and inhibitor development), AEs, serious adverse events (SAEs), and adverse reactions (ARs). Secondary objective is: • To monitor the clinical effects of long-term exposure of prophylaxis 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	HA-SAFE 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 planned to be conducted in multiple countries in Europe. At study start, retrospective data will be collected on the patients' 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, and inhibitor development, other AEs, SAEs and drug-related ARs in standard clinical practice. Adverse reactions (ARs) relating to the system organ classes of the nervous system and psychiatric disorders will be recorded. The planned observation period for each of at least 50 patients will be 4 years, all patients will stay in the study until completion of the overall study. Data collection will occur continuously throughout the patient's observational period (i.e., each visit or assessment will be documented in the eCRF/EDC system as they occur).
Population	All PTPs with hemophilia A receiving prophylaxis with damoctocog alfa pegol will be eligible to be enrolled in the

	study. Indications and contra-indications according to the local market authorization will be carefully considered 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 Jivi prophylaxis treatment • Negative FVIII inhibitor test before study entry • Decision to initiate treatment with commercially available Jivi has been made by the treating physician before and independently from the decision to include the patient in this study Exclusion criteria: • Known or suspected contraindications to Jivi 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
Variables	The variables for the primary objective are: • 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. • Date of inhibitor measurement (if collected). • Inhibitor (no/yes) (if collected). • Titer of inhibitor (Bethesda units) (if collected).

	The variables for the secondary objective are: Laboratory parameters (including date of test), if collected in routine clinical practice at the physician's discretion: • Biochemistry parameters: o Sodium, potassium, albumin, creatinine, bilirubin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyl transferase (GGT), alkaline phosphatase, C-reactive protein (CRP), urea, estimated glomerular filtration rate (eGFR). • Urinalysis parameters: o 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 four extremities), reflexes, sensory aspects, gait, coordination and fine motor function, mental state. • For children: evaluation of appearance, language, social interaction.
Data sources	Historical data based on medical records or on information provided by the patient during routine clinical visits. Treatment-related data documented during visits that take place in routine practice.
Study size	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.
Data analysis	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 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, median, quartiles, and maximum). Continuous

	variables will be described by absolute value and as change from baseline per analysis time point, if applicable.
Milestones	First patient first visit: Q2 2020 Last patient first visit: planned Q2 2023 Last patient last visit: planned Q2 2028 Final report: planned Q4 2028

5. Amendments

None.

6. Milestones

Table 1 presents the planned milestones for the project. These milestones are based on a timely review and approval of the project. Administrative changes to milestones due to delays in study preparation and enrolment do not require amendments to the protocol. Revised study timelines and milestones which do not constitute a need for a formal protocol amendment are kept as stand-alone document (Table 3) that is available upon request.

Table 1: Milestones

Milestone	**Planned date**
Start of data collection (First Patient First Visit)	Q2 2020
End of data collection (Last Patient Last Visit)	Q2 2028
Annual Interim Report	2021 - 2027
Registration in the EU PAS register	Q2 2020
Database clean	Q3 2028
Final statistical analysis	Q4 2028
Final report of study results	Q4 2028

7. Rationale and background

7.1 Epidemiology, classification, and treatment of hemophilia A

Hemophilia A is an X-linked, inherited, genetic bleeding disorder characterized by the deficiency of clotting factor VIII (FVIII) [1],[2]. Hemophilia A comprises approximately 80% of all hemophilia cases, with an annual incidence of approximately 1 in 5,000 live male births [1],[2]. All races and economic groups are affected equally [2]. Prevalence estimates vary by country, ranging between 5 and 21 cases per 100,000 male births. According to the World Federation of Hemophilia, it is estimated that only between 25% and 30% of hemophilia patients globally are adequately diagnosed and managed [3]. Furthermore, up to 75% of hemophilia patients globally live in developing countries in which access to specialist health care professionals and modern therapies prove to be a substantial barrier.

Normal FVIII levels vary between 50% and 150%. The severity of hemophilia A is classified by the amount of clotting factor present in the blood: mild, if the patient has >5% normal clotting factor (>0.05 international units [IU]/mL); moderate, if the patient has between 1% and 5% (≥0.01 to 0.05 IU/mL) normal clotting factor; and severe, if the patient has <1% (<0.01 IU/mL) normal clotting factor. Patients with mild or moderate hemophilia A typically have bleeds only following trauma and tend to report fewer major health-related quality of life impacts. It is estimated that between 60% and 70% of patients with hemophilia A have the severe form of the disease [4]. For these patients, bleeding events often spontaneously occur in joints or muscles or with minimal or unknown trauma to the affected area [5]. Recurrent bleeding in the joints can lead to progressive joint damage, loss of joint mobility, and chronic pain.

The two main approaches to treatment are on-demand therapy, in which the patient is treated in response to a bleed, or prophylactically, in which the patient is treated regularly to prevent bleeding episodes. Prophylaxis is now considered the standard of care in many countries, especially in the pediatric and adolescent population, as it has been shown to reduce complications from repeated bleeds, particularly joint arthropathy [1].

7.2 Rationale

Damoctocog alfa pegol is a B-domain–deleted recombinant factor VIII (BDD-rFVIII) that is site-specifically conjugated with a 60-kDa branched polyethylene glycol (PEG) molecule at a cysteine that has been introduced into the A3 domain (K1804C) resulting in 1 PEG per BDD-rFVIII protein [6]. This addition of PEG prolongs the duration of FVIII in circulation while retaining its full coagulant activity [7],[8]. Damoctocog alfa pegol (Jivi) is approved for prophylaxis and treatment of bleeds in previously treated patients (PTPs) with hemophilia A aged ≥12 years, with a two times per week, every five days or every seven days dose that allows for the treatment regimen to be tailored to individual patient needs. An enhanced pharmacokinetic (PK) profile enables a potentially decreased dosing frequency compared with unmodified rFVIII. 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 [9],[10].

The aim of the proposed study is to characterize in a real-world setting the long-term safety of damoctocog alfa pegol drug usage. The study design will allow for fulfilling the post-approval commitment to the European Medicines Agency (EMA). In accordance with the EMA requirements regarding sample size and observation time, the study aims to observe 50 patients for at least 4 years

each. Detailed information will be collected on reported adverse events (AEs) of special interest including hypersensitivity reactions, loss of drug effect, renal impairment, neurocognitive disorders, inhibitor development, and serious adverse events (SAEs). These parameters will assess if there are any potential safety risks of long-term PEG exposure. The AEs of hypersensitivity and loss of drug effect are related to the class of FVIII replacement therapy. Since damoctocog alfa pegol is a PEGylated product, immunogenicity related to the PEG component can occur. Although the 60 kDa PEG that is part of the damoctocog alfa pegol molecule is larger than the 20-40 kDa PEG moieties on other FVIII replacement products, the low content of PEG associated with the site-specific PEGylation of damoctocog alfa pegol results in a lower PEG load (PEG amount per treatment or per week) and consequently in plasma and tissues relative to some other PEGylated products. The preclinical toxicology studies demonstrated an absence of any pathological effects. The low peak plasma level of approximately 0.1 mg/L at steady state in humans is consistent with these pre-clinical data. No increase in PEG plasma levels has been observed in the clinical studies including the extension studies in more than 100 patients with a total treatment period of at least 3 years up to 6 years[1].

The results of this observational study aim to add to the knowledge of the safety profile of real-world prophylaxis with damoctocog alfa pegol.

Prior to finalization of the present HA-SAFE protocol v1.0, protocol version 0.5 was endorsed by the PRAC on 28 November 2019 (as confirmed in the outcome letter dated 05 December 2019).

7.3 Background

Prophylaxis with FVIII reduces bleeds and improves joint outcomes in patients with severe hemophilia A [11],[12],[13],[14], and it is, therefore the standard of care in most developed countries [1],[15]. However, adherence to prophylaxis is poor in some patients [16]. This may be due to the high time burden and inconvenience of a typical prophylaxis regimen, which requires intravenous infusion at least 2 or 3 times per week [17],[18],[19]. Thus, prolonged–half-life FVIII products that allow for less frequent, individualized dosing may increase adherence and ultimately lead to improved clinical outcomes, including prevention of joint disease [20],[21],[22].

In a phase I study of 14 patients, damoctocog alfa pegol had a half-life of ~19 hours versus ~13 hours for sucrose-formulated rFVIII [7]. In the phase II/III PROTECT VIII study [10] safety was comparable to that observed with other FVIII products [23],[24],[25],[26],[27]. Patients and physicians can choose from 3 effective prophylaxis regimens with damoctocog alfa pegol based on individual patient bleeding profile and lifestyle. However, outside of the clinical study, there are currently little real-world safety data on the use of the product.

8. Research questions and objectives

8.1 Primary objective

The primary objective of this study is:

[1] Bayer Data on File

- 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 PEG accumulation (hypersensitivity reactions, loss of drug effect, renal impairment, neurocognitive disorders, and inhibitor development), AEs, serious adverse events (SAEs), and adverse reactions (ARs).

8.2 Secondary objective(s)

The secondary objective of this study is:

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

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 planned to be 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 transaminase (ALT), aspartate aminotransferase (AST), bilirubin), PEG-plasma level and abnormal findings from neurological assessments will be captured in the eCRF/EDC system. Adverse reactions (ARs) relating to the system organ classes 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 observational 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.

Interim reports will be provided annually to the competent authorities as specified in the milestones.

9.1.1 Primary endpoint

The primary endpoint is:

- Occurrence, duration, treatment, seriousness, and outcome of AEs[2], SAEs, ARs, and FVIII inhibitor from study start to end of study

9.1.2 Secondary endpoints

The secondary endpoints are:

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

9.2 Setting

9.2.1 Eligibility

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 (see section 9.2.4). 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.

9.2.1.1 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 Jivi prophylaxis treatment
- Negative FVIII inhibitor test before study entry

[2] AEs including, but not limited to, hypersensitivity reactions, loss of drug effect, renal impairment, neurocognitive disorders and inhibitor development.

- Decision to initiate treatment with commercially available Jivi has been made by the treating physician before and independently from the decision to include the patient in this study

9.2.1.2 Exclusion criteria

- Known or suspected contraindications to Jivi 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

9.2.2 Withdrawal

In this observational study, withdrawal from the study is independent of the underlying therapy and will not affect the patient's medical care. Each patient may withdraw from the study at any time and without giving a reason. If a patient/legal representative (in case of minors) wants to terminate study participation, no further data will be collected. In case a patient/legal representative would like to withdraw the consent given earlier, s/he should inform his/her doctor and the site should document the withdrawal in the electronic Case Report Form (eCRF) as well as in the patient medical records.

9.2.3 Replacement

Enrollment will stop as outlined in the milestones or when the target sample size is reached. Patients who drop out after the end of enrollment (e.g. withdrawal, lost to follow-up) will be replaced to ensure that all in all 50 patients have reached a minimum follow-up of 4 years.

9.2.4 Representativeness

The eligibility criteria have been selected to allow for a broad representation of patients within the study. The study will enroll previously treated hemophilia A patients initiating or currently receiving prophylaxis damoctocog alfa pegol. Prophylaxis therapy is the recommended standard of care for patients with severe disease and those with moderate disease with a severe patient bleeding profile. By enrolling all eligible patients with mild, moderate or severe disease consecutively, the study will capture real-world data.

Previously untreated hemophilia A patients are not eligible for this study as the safety of damoctocog alfa pegol in this patient population has not been established. Given the incidence rate of hemophilia A, 1 in 5,000 live male births, previously untreated patients represent approximately 2% of the hemophilia patient population. Thus, the study population is broadly representative of mild, moderate, and severe hemophilia A patients, even when previously untreated patients are excluded.

In addition, the inclusion of a representative sample of study sites (i.e., health care providers, hospitals, etc.) in terms of geography, practice size, and academic or private practice type is aimed as a measure to enhance the generalizability of study results. Nevertheless, the final sample of study sites will strongly depend on the willingness of physicians to participate in the study.

The patients documented in the study should be selected based only on eligibility according to a minimal set of selection criteria (see sections 9.2.1.1and 9.2.1.2). No further selection should be

applied, thus increasing the generalizability of the study results. Physicians will be asked to sample consecutive patients whenever possible. This consecutive sampling approach is intended to reduce selection bias by the treating physicians in relation to which patients they enroll in the study, especially with regard to factors that may be associated to the outcome or prognosis of those patients (e.g., demographic characteristics, multiple co-morbidities, as well as concomitant medications), thus maintaining the observational character and enhancing the external validity of the study. Furthermore, an anonymous patient log file (integrated into the Electronic Data Capture [EDC] system) will be used by each site to document patients not enrolled in the study (without recording patient-specific data), including the reason for not enrolling (e.g., refused consent, eligibility criteria not met, etc.).

9.2.5 Visits

The physician documents a first visit that corresponds to the initiation of the observational period (initial visit/baseline) in the eCRF/EDC system. Follow-up visits occur during routine practice – in this non-interventional study, 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 2.

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 (see section 10.4). 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 observational 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 2: Overview of information collected during the initial visit and at subsequent follow-up visits

	Enrollment / Initial visit	**Follow-up visit (including end of observation)**
Eligibility assessment[3]	x	
Date of visit	x	x
Date of informed consent	x	
Demographic data[4] (e.g. date of birth or age; ethnicity, race)	x	
Hemophilia disease history, mutation genotype	x	
Hemophilia treatment history (including Damoctocog alfa pegol history, if any)	x	
Medical history and concomitant diseases	x	
Physical examination (e.g. weight, height, vital signs)][5]	x	x
Prior and concomitant medications	x	x

[3] Including confirmation of eligibility criteria or documentation of reason for non-enrolment, where applicable (see 9.2.4)

[4] 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

[5] If available (i.e. if conducted during routine clinical examination).

	Enrollment / Initial visit	**Follow-up visit (including end of observation)**
Currently prescribed damoctocog alfa pegol regimen	x	x
Damoctocog alfa pegol dose/regimen changes, treatment switches		x (continuous collection)
Damoctocog alfa pegol pharmacokinetic analysis[5]	x	x
Adverse events, Serious adverse events and Adverse reactions (includes systematically collected AEs and AEs of special interest)[6,7]	x (continuous collection)	
FVIII inhibitor[5]	x	x
Biochemistry[5,8]	x	x
Urinalysis[5,9]	x	x
PEG-plasma[5,6]	x	x
Neurological assessment[5,10]	x	x
Number of bleeding episodes	x	x
Reason(s) for end of observation		x (at occurrence)

9.3 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 (see section 9.2.5). In this non-interventional study, the visits are not scheduled by the study team (i.e. visits occur at the physicians' discretion and independent of the

[6] Events up to 30 days after the last dose of damoctocog alfa pegol within the study period.

[7] Including duration, treatment, seriousness and outcome.

[8] Sodium, potassium, albumin, creatinine, bilirubin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyl transferase (GGT), alkaline phosphatase, C-reactive protein (CRP), urea, estimated glomerular filtration rate (eGFR).

[9] Urine albumin/creatinine ratio, spot urine dipstick test.

[10] Including (for all ages) level of consciousness, cranial nerves, body tone, strength (of the four 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.

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). The physician documents the study-relevant data for each patient in the eCRF/EDC system. The pCRF (paper version of the eCRF) is kept as a stand-alone document (see Table 3) and is available upon request.

This is a non-interventional study 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. Nevertheless, if they were collected in local routine clinical practice at the investigator's discretion, all results will be documented in the eCRF/EDC system. In the case that an investigator wants to determine the PEG levels in plasma, 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.

All variables that are available should be recorded by physicians (in the eCRF/EDC); the importance of obtaining complete data (as complete as possible given the non-interventional nature of the study) will be highlighted to the physicians when they are trained prior to study start.

A detailed list of variables collected in this study is kept as a stand-alone document and is available upon request (Table 3)

9.3.1 Variables to determine the primary endpoint

(Serious) adverse events need to be collected as described in section 11.2. Information 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).

9.3.2 Variables to determine the secondary endpoints

The main variables for determination of the secondary endpoints comprise variables to be collected on laboratory tests:

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, aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyl transferase (GGT), alkaline phosphatase, C-reactive protein (CRP), urea, estimated glomerular filtration rate (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 four extremities), reflexes, sensory aspects, gait, coordination and fine motor function, mental state.
- For children: evaluation of appearance, language, social interaction.

9.4 Data sources

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 are able to 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.

9.5 Study size

The study aims to observe 50 patients for at least 4 years each, in line with the sample size, requested the safety analysis by the Authority (EMA). Assuming a dropout rate of approximately

20% (due to lost to follow-up cases or withdrawals), 60 patients will be enrolled. 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%, there is a 64% chance of observing at least one event in a sample of 50 patients.

9.6 Data management

Physicians document the confirmation of the eligibility criteria and the study-relevant data for each patient in the eCRF/EDC system. The pCRF (paper version of the eCRF) is available upon request (see Table 3).

A CRO will be selected and assigned for EDC system development. The eCRF will be part of the EDC system which allows documentation of all outcome variables and covariates by all participating sites in a standardized way. Information on the EDC system is available upon request (see Table 3). Detailed information on data management, including procedures for data collection, retrieval, and preparation are given in the Data Management Plan (DMP), which is available upon request (see Table 3).

For information on quality control, refer to section 9.8.

9.7 Data analysis

9.7.1 Statistical considerations

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 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, median, quartiles, and maximum). Continuous variables will be described by absolute value and as change from baseline per analysis time point, if applicable.

All analyses will be performed for the total study population (overall analysis).

Sample size and disposition information including reasons for discontinuation by analysis time point will be displayed in a frequency table.

All therapies documented in the following forms will be coded using the World Health Organization Drug Global.

- Prior and concomitant medication

Any diagnoses/diseases/event terms documented in the following forms will be coded using the latest Medical Dictionary for Regulatory Activities (MedDRA) version:

- General medical/surgical history
- Adverse events

Interim reports will be provided annually to the competent authorities as specified in the milestones. The final analysis will be performed after the end of the study, which is the date the analytical dataset is completely available.

All statistical details including calculated variables and proposed format and content of tables will be detailed in the Statistical Analysis Plan (SAP). Bayer Consumer Care AG will provide oversight of data analysis activities that will be assigned to a CRO. All specific processes and technical details will be documented by the CRO statistician in the SAP and tables specification manual. The SAP will be finalized before the first database lock. The SAP will be available upon request (see Table 3).

Analysis populations:

The Safety Analysis Set (SAF) include all patients who took at least 1 dose of damoctocog alfa pegol in the study

Missing data:

Because the aim of this study is to obtain data under conditions of routine clinical care (i.e., naturalistic settings), some patients may have missing values for some variables. To address missing data, the following strategy will be applied:

- In general, clinical outcomes collected in the study will not be imputed.
- Imputation rules for missing/incomplete dates will be defined in the SAP.

The SAP will describe in detail the methods and variables used in the analyses, including those pertaining to truncated and missing data. Furthermore, the extent of missing or truncated data within the analysis datasets will be described in the final study report.

Exposure risk-window for safety analysis:

Patients may switch damoctocog alfa pegol treatment regimen and/or may permanently discontinue from damoctocog alfa pegol treatment during the study. In general, only the patient time during which patients are receiving treatment with prophylactic damoctocog alfa pegol will be included in the person-years denominator when estimating rates of safety outcomes for prophylactic damoctocog alfa pegol.

9.7.2 Analysis of population characteristics

Population characteristics including demographics and baseline characteristics will be analyzed descriptively and presented as summary statistics or frequency tables. Some continuous variables will be categorized and presented in frequency tables in addition to summary statistics if applicable. Categories will be defined in the SAP. Prior and concomitant medications/treatments and medical history will be presented by frequency tables.

9.7.3 Analysis of primary variable(s)

The analysis described in this section will be performed based on adverse events (AEs) on the SAF.

An overview table displaying all AEs will be presented. This overview table will provide a summary on patient-level:

- Any event (AE of special interest, AE, SAE, and AR).

- Maximum intensity of events.
- Events with the outcome of death.
- Events leading to a change of treatment regimen of study treatment.
- Events leading to discontinuation of study treatment.
- Events related to inhibitor development.

AEs will be coded using the latest version of MedDRA. A summary of AEs will be presented by the primary System Organ Class (SOC) and Preferred Term (PT). AEs will primarily be classified by MedDRA PT. Aggregated incidences at the SOC level will also be presented.

Each of the AEs of special interest will be described separately. Event rates and 95% CIs will be reported as both incidence risks and exposure-adjusted incidence rates per patient.

Additionally, a detailed listing will be provided for AEs related to the development of an inhibitor or positive inhibitor measurements, including information on the history of inhibitors.

9.7.4 Analysis of secondary variables

Laboratory parameters will be analyzed descriptively. Results will be displayed by summary statistics and as change from baseline.

A descriptive analysis will be performed for the number of patients with laboratory parameters outside of the normal ranges.

9.7.5 Analysis of safety data

All safety variables are indicated as primary and secondary outcomes and will be analyzed as described in sections 9.7.3 and 9.7.4, respectively.

9.8 Quality control

9.8.1 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. Physicians will have the chance to discuss and develop a common understanding of the study protocol and the eCRF. Patients will be trained by the site personnel on how to complete the patient diary.

A CRO will be selected and assigned for EDC system development, quality control, verification of the data collection, data analysis and data transfer to Bayer Consumer Care AG.

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) which is available on request (see Table 3). Operational measures which will positively impact data quality will be considered as required.

All observations will be recorded in a standardized eCRF. 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 DMP. The DMP will specify measures for handling of missing data and permissible clarifications. The DMP is available upon request (see Table 3).

Medical review of the data will be performed according to the Medical Review Plan (MRP). The purpose of the medical review is to verify the data from a medical perspective for plausibility, consistency, and completeness and to identify potential issues that could affect the robustness of the collected study data or the progress of the study. Detailed information on the Medical Review will be described in the MRP, which is available upon request (see Table 3).

National and international data protection laws, as well as regulations on non-interventional studies, will be followed. Electronic records used for capturing patient data (eCRF) will be validated according to 21 Code of Federal Regulations (CFR) Part 11 (US Food and Drug Administration [FDA]) [28]. 21 CFR Part 11 regulations describe the criteria to consider electronic records including e-signatures to be reliable and generally equivalent to paper records and handwritten signatures. They mandate access controls to ensure that only authorized individuals can use the system, additionally a computer-generated audit trail has to be in place to record the date and time of any actions to create, modify, or delete electronic records. The documentation is available upon request (see Table 3).

9.8.2 Quality review

Quality review will be performed in 2 steps: in the first step, the site's training status will be assessed via standardized telephone interviews. Hereby, it can be assured that the investigator and site personnel is aware of the required collection of all available data on hepatic and renal function as well as neurological assessments.

In the second step regular on-site source data verification will be conducted by trained personnel (e.g. CRAs). 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 Quality Review Plan (QRP), which is available upon request (see Table 3).

9.8.3 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.

9.8.4 Certification/qualification of external parties

Not applicable.

9.9 Limitations of the research methods

In general, because of the non-interventional study design 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. Furthermore, due to the study being non-interventional, the information to be collected is limited to and depending on the visits/assessments occurred in routine clinical practice. Therefore, it cannot be forced that complete data on hepatic and renal function and neurological assessments will be available for final analyses as the performance of these assessments is highly depending on the physician's discretion. Nevertheless, any clinically relevant change in organ functions or development of new symptoms would be documented as AE and would trigger lab assessments in routine clinical practice.

The sample size is not large enough to observe rare AEs. Furthermore, if a rare AE is observed, the sample size is not large enough to draw any conclusions on the association. It may include limited availability of treatment data and underreporting of safety outcomes if a patient leaves the study and/or is not possible to be followed-up adequately (e.g., withdrawal of consent or loss to follow-up).

9.10 Other aspects

Not applicable.

10. Protection of human subjects

10.1 Ethical conduct of the study

This study is a non-interventional study where damoctocog alfa pegol is prescribed in a customary manner in accordance with the terms of the marketing authorization. There is no assignment of a patient to a particular therapeutic strategy. The treatment decision falls within current practice and the prescription of the medicine is clearly separated from the decision to include the patient in the study. No additional diagnostic or monitoring process is required for participation or during the study. Epidemiological methods will be used for the analysis of the collected data.

10.2 Regulatory authority approvals/authorizations

The study will be carried out within an approved indication in accordance with guidelines and regulations of EMA, FDA, and applicable local law(s) and regulation(s) (e.g., European Union [EU] Regulation No 520/2012 [29]). Recommendations given by other organizations will be followed as well (e.g., European Federation of Pharmaceutical Industries and Associations [EFPIA] [30], European Network of Centers in Pharmacoepidemiology and Pharmacovigilance [ENCePP] [31]).

In addition, the guidelines on Good Pharmacovigilance Practices (GVP module VI [32] and since the study qualifies as a Post-Authorization Safety Study (PASS), GVP module VIII [33],[34]) will be followed.

10.3 Independent ethics committee (IEC) or institutional review board (IRB)

In all countries where reference to an IEC/IRB is required, documented approval from appropriate IECs/IRBs will be obtained for all participating sites prior to study start. When necessary, an extension, amendment or renewal of the IEC/IRB approval must be obtained and also forwarded to Bayer Consumer Care AG. The IEC/IRB must supply to Bayer Consumer Care AG, upon request, a list of the IEC/IRB members involved in the vote and a statement to confirm that the IEC/IRB is organized and operates according to applicable laws and regulations.

10.4 Patient information and consent

Before documentation of any data, informed consent is obtained by the patient/legal representative in writing. For patients under legal age at the time of enrollment, signed assent by the patient and parental/legal guardian signed informed consent will be obtained. In countries where required by law or regulation, the physician must have the IEC/IRB written approval/favorable opinion of the written informed consent form and any other written information to be provided to patients prior to the beginning of the observation.

10.5 Patient insurance

In this observational study, data on routine treatment of patients in daily practice are documented and analyzed with the help of epidemiological methods. Treatment including diagnosis and monitoring of therapy follows exclusively routine daily practice. Current medical daily practice is observed, and for the patient no risks beyond regular therapy exist – there is no additional hazard arising from study participation. As no study-related risks exist, there is no need to protect the patient additionally with patient insurance. The general regulations of medical law and the professional indemnity insurance of the physicians and, respectively, the institutions involved provide sufficient protection for both patient and physician.

No study treatment will be provided to patients. Thus, product insurance is covered by the existing product liability.

10.6 Confidentiality

Bayer Consumer Care AG, as well as all physicians, ensure adherence to applicable data privacy protection regulation. Data are transferred in encoded form only. The entire documentation made available to Bayer does not contain any data which, on its own account or in conjunction with other freely available data, can be used to re-identify natural persons. The physicians are obligated to ensure that no documents contain such data.

All records identifying the patient will be kept confidential and will not be made publicly available. Patient names will not be supplied to Bayer Consumer Care AG. If the patient name appears on any document, it must be obliterated before a copy of the document is supplied to Bayer Consumer Care AG. Study findings stored on a computer will be stored in accordance with local data protection laws.

The physician will maintain a list to enable patients' records to be identified in case of queries. In case of a report of an SAE, the responsible pharmacovigilance person may ask for additional clarification. In that case, the company is not allowed to directly contact the patient. All additional information will be provided by the physician.

11. Management and reporting of adverse events/adverse reactions

11.1 Definitions

An Adverse Event (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 [35].

The term also covers laboratory findings or results of other diagnostic procedures that are considered to be clinically relevant (e.g., that require unscheduled diagnostic procedures or treatments or result in withdrawal from the study).

- The AE may be:
- A new illness.
- Worsening of a sign or symptom of the condition under treatment or of a concomitant illness.
- An effect of the study treatment.
- An effect of a concomitant medication or treatment.
- Off label use[11], occupational exposure, lack of drug effect, medication error, overdose, drug abuse, drug misuse or drug dependency itself, as well as any resulting event.
- An effect related to pre-existing condition improved (unexpected therapeutic benefits are observed).
- Product exposure via mother/father (exposure during conception, pregnancy, childbirth, and breastfeeding).

As mentioned above no causal relationship with a product is implied by the use of the term “adverse event”.

An Adverse Reaction (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.

Causal relationship: The assessment of the causal relationship between an AE and the administration of treatment is a clinical decision based on all available information at the time of the completion of the eCRF. The assessment is based on the question of whether there was a “reasonable causal relationship” to the study treatment in question. Possible answers are “yes” or “no”.

An assessment of "no" would include:

- The existence of a clear alternative explanation (e.g., mechanical bleeding at the surgical site).

[11] According to GVP Module VI, off label use “relates to situations where the medicinal product is intentionally used for a medical purpose not in accordance with the authorized product information”. Off label use *per se* is an AE, even if no AR is reported, therefore it needs to be ensured that all relevant variables to identify such potential incidents are collected (e.g., indication)

- Non-plausibility (e.g., the patient is struck by an automobile when there is no indication that the product caused disorientation that may have caused the event; cancer developing a few days after the first treatment administration).

An assessment of "yes" indicates that there is a reasonable suspicion that the AE is associated with the use of the study treatment. Factors to be considered in assessing the relationship of the AE to study treatment include:

- The temporal sequence from product administration: The event should occur after the product is given. The length of time from product exposure to the event should be evaluated in the clinical context of the event.
- Recovery on product discontinuation (de-challenge), recurrence on product re-introduction (re-challenge): Patient's response after de-challenge or patient's response after re-challenge should be considered in the view of the usual clinical course of the event in question.
- Underlying, concomitant, intercurrent diseases: Each event should be evaluated in the context of the natural history and course of the disease being treated and any other disease the patient may have.
- Concomitant medication or treatment: The other products the patient is taking or the treatment the patient receives should be examined to determine whether any of them may be suspected to cause the event in question.
- The pharmacology and PK of the study treatment: The PK properties (absorption, distribution, metabolism, and excretion) of the study treatment, coupled with the individual patient's pharmacodynamics should be considered.

An AE or AR is serious (SAE) if it:

- Results in death.
- Is life-threatening.
- Requires in-patient hospitalization or prolongation of existing hospitalization (see exceptions below).
- Results in persistent or significant disability or incapacity.
- Is a congenital anomaly or birth defect.
- Is medically important.

Death is usually the outcome of an underlying clinical event that causes it. Hence, it is the cause of death that should be regarded as an SAE. The 1 exception to this rule is "sudden death" where no

cause has been established. In this instance, "sudden death" should be regarded as the AE and "fatal" as its reason for being "serious".

Life-threatening: The term "life-threatening" in the definition of "serious" refers to an AE in which the subject was at risk of death at the time of the event. It does not refer to an AE which hypothetically might have caused death if it were more severe.

Hospitalization: Any AE leading to hospitalization or prolongation of hospitalization will be considered as serious unless the admission was:

Planned before patient's inclusion in the study (i.e., elective or scheduled surgery); or Ambulant (shorter than 12 hours); or Part of the normal treatment or monitoring of the studied disease (i.e., not due to a worsening of the disease).

However, it should be noted that invasive treatment during any hospitalization may fulfill the criteria of "medically important" and as such may be reportable as an SAE dependent on clinical judgment. In addition, where local regulatory authorities specifically require a more stringent definition, the local regulation takes precedence.

Disability means a substantial disruption of a patient's ability to conduct normal life functions.

Congenital anomaly (birth defect), i.e., any congenital anomaly observed in an infant, or later in a child, should be regarded as an SAE when:

- The mother had been exposed to a medicinal product at any stage during conception or pregnancy or during delivery.
- The father was exposed to a medicinal product prior to conception.

Other medically important serious event: Any AEs may be considered serious as it may jeopardize the patient and may require intervention to prevent another serious condition. Medically important events either refer to or might be indicative of a serious disease state. Such reports warrant special attention because of their possible association with serious disease state and may lead to more decisive action than reports on other terms.

11.2 Collection

It should be documented in the eCRF whether the patient is participating in a registry or other program where reporting of AEs to a third party may occur in addition to the reporting requirements for this study.

Starting with the first administration of damoctocog alfa pegol after enrollment into the study, all non-serious AEs must be documented on the AE Report Form or in the eCRF/EDC system and forwarded to the Marketing Authorization Holder (MAH) within 7 calendar days (for EU countries or if required by local regulations of participating country) or 60 days (for countries outside the EU) of awareness. All SAEs must be documented and forwarded immediately (within 1 business day of awareness). For each AE, the physician must assess and document the seriousness, duration, relationship to the product, action taken and outcome of the event.

If a pregnancy in the female partner of a male patient or in a female patient occurs during the study, although it is not an SAE itself, it should be documented and forwarded to the MAH within the same time limits as an SAE. The result of pregnancy will be followed-up according to applicable Bayer

standard operating procedures. Any data on abnormal findings concerning either the mother or the baby will be collected as AEs.

The documentation of any AE/SAE ends at the latest 30 days after the completion of the observation period of the patient: i.e., any AE/SAE - regardless of the relationship and the seriousness - occurring up to 30 days after the last dose of damoctocog alfa pegol within the patient's observation period has to be documented and forwarded to the MAH within the given timelines.

As long as the patient has not received any damoctocog alfa pegol within the frame of the study AEs/SAEs do not need to be documented as such in this non-interventional study. However, they are part of the patient's medical history.

For any serious product-related AE occurring after study end, the standard procedures that are in place for spontaneous reporting have to be followed.

11.3 Management and reporting

Non-serious AEs

The outcome of all reported AEs will be followed-up and documented. Where required, physicians might be contacted directly by the responsible study staff to provide further information.

Non-serious ARs

All non-serious ARs occurring under treatment with damoctocog alfa pegol that qualifies for expedited reporting will be submitted to the relevant authorities according to EU pharmacovigilance legislation (Regulation [EU]) No 1235/2010 and Directive 2010/84/EU, Module VI [32]) and according to national regulations by the MAH; however, all physicians must obey local legal requirements.

For non-serious ARs occurring under non-Bayer products, the physician has to account for and comply with the reporting system of the product's MAH within the frame of local laws and regulations as well as other locally applicable laws and regulations.

Serious AEs

Any SAE or pregnancy entered into the eCRF/EDC system will be forwarded immediately (within 1 business day of awareness) to the pharmacovigilance country person responsible for SAE processing. The outcome of all reported SAEs (resolution, death, etc.) will be followed-up and documented. Where required, physicians might be contacted directly by the pharmacovigilance country person in charge to provide further information.

Submission to the relevant authorities according to national regulations will be performed by the MAH for SAEs related to damoctocog alfa pegol treatment; however, all physicians must obey local legal requirements.

For any serious drug-related AE occurring after study end, the standard procedures that are in place for spontaneous reporting have to be followed.

For SAEs that occurred while administering non-Bayer products, the physician has to account for and comply with the reporting system of the product's MAH within the frame of local laws and regulations as well as other locally applicable laws and regulations.

Submission of SAEs related to non-Bayer products to the relevant authorities according to national regulations will be performed by the product's MAH.

AEs of special interest:

The following AEs of special interest are reported (if done in routine clinical practice):

- Hypersensitivity reactions including skin-related and systemic reactions, such as anaphylactic reactions (seriousness should be a case-by-case decision).
- Inhibitor development: inhibitors need to be assessed as mandatory serious and reported to Bayer Consumer Care AG, i.e. forwarded immediately (within 1 business day of awareness).
- Loss of drug effect (immune response to PEG, anti-drug antibodies, etc.).
- Renal impairment.
- Neurocognitive disorders.

The reporting physician will be asked to complete additional questionnaires when any of the above AEs of special interest are reported (see Annex 3: Additional information).

Any bleeding event occurring during the study will not be documented as an AE, as long as it is not considered to have a "causal relationship" to the product. If the bleed requires hospitalization, it must be reported as an SAE.

The physician will be asked to document in the eCRF whether the patient participates in any registries whereby AEs could be reported to both the registry and the HA-SAFE study.

11.4 Evaluation

Whenever new important safety information is received, e.g., case reports from a physician, the reports are processed and entered into the global pharmacovigilance safety database. These reports will be reviewed on a regular basis (for information on the collection, management and reporting of case reports, refer to sections 11.2 and 11.3). If a potential safety signal is suspected, an investigation of the suspected potential signal will be performed according to internal standard operating procedures, for further evaluation within the context of benefit-risk.

12. Plans for disseminating and communicating study results

This study will be registered at "www.clinicaltrials.gov" and in the EU PAS register at "http://www.encepp.eu/encepp_studies/indexRegister.shtml". Results will be disclosed in a publicly available database within the standard timelines.

If a regulatory authority requests progress reports these will be provided in agreed frequency and content.

The results of this non-interventional study are intended to be published in a peer-reviewed journal and as abstracts/presentations at medical congresses under the oversight of the MAH. Current guidelines and recommendation on Good Publication Practice (GPP) will be followed (e.g., GPP 2 guidelines [36], Strengthening the Reporting of Observational Studies in Epidemiology [STROBE]

[37]). No individual physician may publish the results of this study, or their own patients, without prior approval from the MAH.

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Annex 1: List of stand-alone documents

Table 3: List of stand-alone documents

Document Name
Investigator list
Country & Site list
Study timelines and milestone update
Paper Case Report Form (pCRF)
Detailed list of variables
Information on Electronic Data Capture (EDC) System
EDC System Validation
Data Management Plan (DMP)
Statistical Analysis Plan (SAP)
Quality Review Plan (QRP)
Medical Review Plan (MRP)

Annex 2: ENCePP checklist for post-authorization safety study (PASS) protocols

ENCePP Checklist for Study Protocols (Revision 4)

Doc.Ref. EMA/540136/2009

Study title:
HA-SAFE: Observational study evaluating long-term safety of real-world treatment with damoctocog alfa pegol in previously treated patients with hemophilia A

EU PAS Register® number: not yet registered
Study reference number (if applicable): n/a

Section 1: Milestones	**Yes**	**No**	**N/A**	**Section Number**
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection[12]	☒	☐	☐	6
1.1.2 End of data collection[13]	☒	☐	☐	6
1.1.3 Progress report(s)	☐	☐	☒	
1.1.4 Interim report(s)	☒	☐	☐	6
1.1.5 Registration in the EU PAS Register®	☒	☐	☐	6
1.1.6 Final report of study results.	☒	☐	☐	6

Comments:

Section 2: Research question	**Yes**	**No**	**N/A**	**Section Number**
2.1 Does the formulation of the research question and objectives clearly explain:	☐	☐	☐	
2.1.1 Why the study is conducted? (e.g. to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue)	☒	☐	☐	7
2.1.2 The objective(s) of the study?	☒	☐	☐	8
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	9
2.1.4 Which hypothesis(-es) is (are) to be tested?	☐	☐	☒	
2.1.5 If applicable, that there is no *a priori* hypothesis?	☒	☐	☐	9.7.1

[12] Date from which information on the first study is first recorded in the study dataset or, in the case of secondary use of data, the date from which data extraction starts.

[13] Date from which the analytical dataset is completely available.

Comments:

This is a prospective, observational study, so no hypothesis is being tested.

Section 3: Study design	**Yes**	**No**	**N/A**	**Section Number**
3.1 Is the study design described? (e.g. cohort, case-control, cross-sectional, other design)	☒	☐	☐	9.1
3.2 Does the protocol specify whether the study is based on primary, secondary or combined data collection?	☒	☐	☐	9.1
3.3 Does the protocol specify measures of occurrence? (e.g., rate, risk, prevalence)	☒	☐	☐	9.7.1
3.4 Does the protocol specify measure(s) of association? (e.g. risk, odds ratio, excess risk, rate ratio, hazard ratio, risk/rate difference, number needed to harm (NNH))	☐	☐	☒	
3.5 Does the protocol describe the approach for the collection and reporting of adverse events/adverse reactions? (e.g. adverse events that will not be collected in case of primary data collection)	☒	☐	☐	11.2, 11.3

Comments:

Statistical analyses will be descriptive and explorative in nature.

Section 4: Source and study populations	**Yes**	**No**	**N/A**	**Section Number**
4.1 Is the source population described?	☒	☐	☐	9.1
4.2 Is the planned study population defined in terms of:				
4.2.1 Study time period	☒	☐	☐	9.1
4.2.2 Age and sex	☒	☐	☐	9.1
4.2.3 Country of origin	☒	☐	☐	9.1
4.2.4 Disease/indication	☒	☐	☐	9.1
4.2.5 Duration of follow-up	☒	☐	☐	9.1
4.3 Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☒	☐	☐	9.2.1

Comments:

Section 5: Exposure definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
5.1 Does the protocol describe how the study exposure is defined and measured? (e.g. operational details for defining and categorising exposure, measurement of dose and duration of drug exposure)	☐	☒	☐	

Section 5: Exposure definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
5.2 Does the protocol address the validity of the exposure measurement? (e.g. precision, accuracy, use of validation sub-study)	☐	☒	☐	
5.3 Is exposure categorised according to time windows?	☐	☐	☒	
5.4 Is intensity of exposure addressed? (e.g. dose, duration)	☒	☐	☐	9.2.5
5.5 Is exposure categorised based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☐	☒	☐	
5.6 Is (are) (an) appropriate comparator(s) identified?	☐	☐	☒	

Comments:

This is a non-interventional study, and all treatment decisions (including dosing and exposure) will be made by the treating physician without influence from the Study Initiator and Funder.

Section 6: Outcome definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
6.1 Does the protocol specify the primary and secondary (if applicable) outcome(s) to be investigated?	☒	☐	☐	9.1
6.2 Does the protocol describe how the outcomes are defined and measured?	☒	☐	☐	9.1, 9.3.1, 9.3.2
6.3 Does the protocol address the validity of outcome measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, use of validation sub-study)	☐	☒	☐	
6.4 Does the protocol describe specific outcomes relevant for Health Technology Assessment? (e.g. HRQoL, QALYs, DALYS, health care services utilisation, burden of disease or treatment, compliance, disease management)	☐	☒	☐	

Comments:

Section 7: Bias	**Yes**	**No**	**N/A**	**Section Number**
7.1 Does the protocol address ways to measure confounding? (e.g. confounding by indication)	☐	☒	☐	
7.2 Does the protocol address selection bias? (e.g. healthy user/adherer bias)	☒	☐	☐	9.9
7.3 Does the protocol address information bias? (e.g. misclassification of exposure and outcomes, time-related bias)	☒	☐	☐	9.9

Comments:

Section 8: Effect measure modification	**Yes**	**No**	**N/A**	**Section Number**
8.1 Does the protocol address effect modifiers? (e.g. collection of data on known effect modifiers, sub-group analyses, anticipated direction of effect)	☒	☐	☐	9.7.1

Comments:

Section 9: Data sources	**Yes**	**No**	**N/A**	**Section Number**
9.1 Does the protocol describe the data source(s) used in the study for the ascertainment of:				
9.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview)	☒	☐	☐	9.4
9.1.2 Outcomes? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics)	☒	☐	☐	9.4
9.1.3 Covariates and other characteristics?	☒	☐	☐	9.3
9.2 Does the protocol describe the information available from the data source(s) on:				
9.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☒	☐	☐	9.4
9.2.2 Outcomes? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	9.4
9.2.3 Covariates and other characteristics? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle)	☒	☐	☐	9.4
9.3 Is a coding system described for:				
9.3.1 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)	☒	☐	☐	9.7
9.3.2 Outcomes? (e.g. International Classification of Diseases (ICD), Medical Dictionary for Regulatory Activities (MedDRA))	☒	☐	☐	9.7
9.3.3 Covariates and other characteristics?	☒	☐	☐	9.7
9.4 Is a linkage method between data sources described? (e.g. based on a unique identifier or other)	☐	☒	☐	

Comments:

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Section Number**
10.1 Are the statistical methods and the reason for their choice described?	☒	☐	☐	9.7
10.2 Is study size and/or statistical precision estimated?	☒	☐	☐	9.7
10.3 Are descriptive analyses included?	☒	☐	☐	9.7
10.4 Are stratified analyses included?	☒	☐	☐	9.7
10.5 Does the plan describe methods for analytic control of confounding?	☐	☒	☐	
10.6 Does the plan describe methods for analytic control of outcome misclassification?	☐	☒	☐	
10.7 Does the plan describe methods for handling missing data?	☒	☐	☐	9.7
10.8 Are relevant sensitivity analyses described?	☒	☐	☐	9.7

Comments:

Section 11: Data management and quality control	**Yes**	**No**	**N/A**	**Section Number**
11.1 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	☒	☐	☐	9.8.3
11.2 Are methods of quality assurance described?	☒	☐	☐	9.8.1
11.3 Is there a system in place for independent review of study results?	☒	☐	☐	9.8.2

Comments:

Section 12: Limitations	**Yes**	**No**	**N/A**	**Section Number**
12.1 Does the protocol discuss the impact on the study results of:				
12.1.1 Selection bias?	☒	☐	☐	9.9
12.1.2 Information bias?	☒	☐	☐	9.9
12.1.3 Residual/unmeasured confounding? (e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods).	☐	☒	☐	
12.2 Does the protocol discuss study feasibility? (e.g. study size, anticipated exposure uptake, duration of follow-up in a cohort study, patient recruitment, precision of the estimates)	☒	☐	☐	9.1, 9.2.5, 9.5

Comments:

Section 13: Ethical/data protection issues	**Yes**	**No**	**N/A**	**Section Number**
13.1 Have requirements of Ethics Committee/ Institutional Review Board been described?	☒	☐	☐	10.3
13.2 Has any outcome of an ethical review procedure been addressed?	☐	☒	☐	
13.3 Have data protection requirements been described?	☒	☐	☐	9.8.1, 10.6

Comments:

Section 14: Amendments and deviations	**Yes**	**No**	**N/A**	**Section Number**
14.1 Does the protocol include a section to document amendments and deviations?	☒	☐	☐	5

Comments:

However, this section is empty since this is the first protocol.

Section 15: Plans for communication of study results	**Yes**	**No**	**N/A**	**Section Number**
15.1 Are plans described for communicating study results (e.g. to regulatory authorities)?	☒	☐	☐	12
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	12

Comments:

Name of the main aut PPD PPD

Date: 13 JAN 2020

Signature: _____

Annex 3: Additional information

Specific adverse drug reaction follow-up questionnaires:

Questionnaire_Hypersensitivity.pdf

Questionnaire_Neurocognitive Disorders.p

Questionnaire_LODE.pdf

Questionnaire_Renal Impairment.pdf

Questionnaire_User Guidance.pdf

Annex 4: Description of amendments

Not applicable.

Annex 5: Signature pages

This protocol is electronically signed in the study management system

Title	HA-SAFE: Observational study evaluating long-term safety of real-world treatment with damoctocog alfa pegol in previously treated patients with hemophilia A
Protocol version and date	v 1.0, 13 JAN 2020
IMPACT study number	20904
Study type / Study phase	Observational, post-approval ☒ PASS Joint PASS: ☐ YES ☒ NO
EU PAS register number	Study not yet registered
Medicinal product / Active substance	Jivi/ ATC code: B02BD02/Hematological/Damoctocog alfa pegol
Study Initiator and Funder	Bayer Consumer Care AG, Basel, Switzerland

The signatories confirm that they agree that the study will be conducted under the conditions described in the protocol.

Signatories

- PPD (Study Conduct Responsible)
- PPD (Qualified Person responsible for Pharmacovigilance (QPPV))
- PPD (Study Medical Expert)
- PPD (MAH contact person; Regulatory Affairs responsible)
- PPD (Study Safety Lead)
- PPD (Study Statistician)
- PPD (Study Data Manager)
- PPD (Study Epidemiologist)
- PPD (Real-World Evidence Strategy Lead)