Post-Authorization Safety Study (PASS) Information

Acronym/Title	HEM-POWR: Observational Study Evaluating Effectiveness and Safety of Real-World Treatment with Damoctocog alfa pegol in Previously Treated Patients with Hemophilia A
Protocol version and date	v 1.1, 18 MAR 2019
IMPACT study number	20002
Study type/Study phase	Observational, post-approval ☐ non-PASS ☒ PASS Joint PASS: ☐ YES ☒ NO
EU PAS register number	Study not yet registered
Active substance	ATC code: B02BD02/Hematological/Damoctocog alfa pegol
Medicinal product	Damoctocog alfa pegol
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 objectives of this study are to assess the effectiveness and long term safety of prophylaxis with damoctocog alfa pegol in the real-world setting through the collection of total bleeding events and analysis of the annualized bleeding rate (ABR) in the different prophylaxis regimens (following approved local label or any other regimen prescribed by the physician as part of normal clinical practice) in patients with hemophilia A. The analyses will be stratified, based on severity of hemophilia, severity of patient bleeding profile, disease characteristics, prophylaxis regimen, age, and time on treatment (i.e., damoctocog alfa pegol-naive or not). In addition, the study will capture patterns of switching in

	damoctocog alfa pegol dose and dosing regimen, reasons for choice of treatment regimen, damoctocog alfa pegol consumption, adverse events, pharmacokinetics (if part of routine practice), as well as patient treatment satisfaction, work productivity and activity impairment. Patients participating in HEMPOWR will be offered to enroll into a sub-study arm evaluating activity with an activity tracking device (ActiGraph; patient will be blinded to the activity tracking device values). The objective of the sub-study is to investigate relationship between patient daily regular activity and efficacy parameters collected from HEM-POWR. Enrollment into HEM-POWR is not influenced by the patient's decision whether to participate in the sub-study or not. Participation in the sub-study is fully voluntary and will not impact the main objectives or data collected in HEM-POWR. Details of the sub-study, including the analysis of the activity data will be described in a separate sub-study protocol as a part of the main study.
Countries of study	The study is planned to be conducted in Austria Belgium/Luxemburg, Brazil, Canada, China, Colombia, Finland, France, Germany, Greece, Italy, Japan, Kuwait, Mexico, Netherlands, Russia, Saudi Arabia, Scandinavia (Denmark, Norway and Sweden), Slovenia, Spain, Switzerland, Taiwan, UAE and USA. The study may also be conducted in other countries not currently listed.
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Marketing authorization holder

Marketing authorization holder(s)	Bayer AG, 51368 Leverkusen, Germany
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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.

1. Table of contents

2. List of abbreviations

ABR	Annualized bleeding rate
AE	Adverse Event
AR	Adverse reaction
ATC	Anatomical Therapeutic Chemical (Classification System)
BDD-rFVIII	B-domain–deleted recombinant factor VIII
CFR	Code of Federal Regulations
CI	Confidence interval
CIQ	Classroom impairment questions
CRO	Contract Research Organization
DMP	Data Management Plan
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EFPIA	European Federation of Pharmaceutical Industries and Associations
EMA	European Medicine Agency
ENCePP	European Network of Centers in Pharmacoepidemiology and Pharmacovigilance
EU	European Union
FAS	Full analysis set
FDA	US Food and Drug Administration
FVIII	Factor VIII
GPP	Good Publication Practice
GVP	Good Pharmacovigilance Practice
HEAD-US	Hemophilia Early Arthropathy Detection with Ultrasound
Hemo-QoL-A	Hemophilia Quality of Life Measure for adults
Hemo-QoL-SF	Hemophilia Quality of Life short form for children
Hemo-SAT A	Hemophilia Treatment Satisfaction Questionnaire for adults
HJHS	Hemophilia Joint Health Score
HS	Hemophilia Specific
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IRB	Institutional Review Board
ITI	Immune tolerance induction

IU	International units
MAH	Marketing Authorization Holder
MedDRA	Medical Dictionary for Regulatory Activities
MRP	Medical Review Plan
OS	Observational Study
PAS	Post-Authorization Study
PASS	Post-Authorization Safety Study
PEG	Polyethylene glycol
PK	Pharmacokinetic
PRO	Patient-reported outcome
PT	Preferred Term
PTP	Previously treated patient
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
SD	Standard deviation
SOC	System Organ Class
STROBE	Strengthening the Reporting of Observational Studies in Epidemiology
TEAE	Treatment-Emergent Adverse Event
WPAI	Work Productivity and Activity Impairment Scale

3. Responsible parties

3.1 Study initiator and funder

Role: OS 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: OS Safety Lead
Name: PPD

Role: OS Medical Expert
Name: PPD

Role: OS Statistician
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Role: OS Data Manager
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Role: OS Epidemiologist
Name: PPD

Role: OS Health Economics and Outcomes Research responsible
Name: PPD

Role: Regulatory Affairs responsible
Name: PPD

Role: OS Real World Evidence Strategy Lead
Name: PPD

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 6) which is available upon request.

Information on the Steering/Publication Committee Members and the respective Charters are kept as stand-alone documents (see Table 6) which are 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	HEM-POWR: Observational Study Evaluating Effectiveness and Safety of Real-World Treatment with Damoctocog alfa pegol in Previously Treated Patients with Hemophilia A
Protocol version and date	v 1.1, 18 MAR 2019
IMPACT study number	20002
Study type/Study phase	Observational, Post-approval ☐ non-PASS ☒ PASS Joint PASS: ☐ YES ☒ NO
Author	PPD
Rationale and background	Hemophilia A is an X-linked, inherited, genetic bleeding disorder characterized by 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 inhabitants. All races and economic groups are affected equally. Prevalence estimates vary by country, ranging between 5 and 21 cases per 100,000 male inhabitants. Damoctocog alfa pegol is intended for prophylaxis and treatment of bleeds in previously treated patients (PTPs) with hemophilia A aged ≥12 years, with a predictable weekly 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 recombinant clotting FVIII. Efficacy and safety of prophylaxis dosing with damoctocog alfa pegol was 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 the proposed study is to characterize in a real-world setting the effectiveness and long term safety of damoctocog alfa pegol drug usage. These results can be used to educate patients, payors and providers about real-world prophylaxis dosing regimens with damoctocog alfa pegol. Patients participating in HEM-POWR will be offered to enroll into a sub-study arm evaluating activity with an activity tracking device (type of Actigraph or similar; patient will be

	blinded to the activity tracking device values). The objective of the sub-study is to investigate relationship between patient daily regular activity and efficacy parameters collected from HEM-POWR. Enrollment into HEM-POWR is not influenced by the patient's decision whether to participate in the sub-study or not. Participation in the sub-study is fully voluntary and will not impact the main objectives or data collected in HEM-POWR. Details of the sub-study, including the analysis of the activity data will be described in a separate sub-study protocol as a part of the main study.
Research question and objectives	The primary objective in this study is: • To assess the effectiveness of prophylaxis with damoctocog alfa pegol in the real-world setting through the collection of total bleeding events and analysis of annualized bleeding rate (ABR) in the different prophylaxis regimens (following approved local label) in patients with hemophilia A. The secondary objectives in this study are to: • Assess the long term safety of prophylaxis with damoctocog alfa pegol in the real-world setting through the collection and analysis of adverse events (AEs) of special interest (hypersensitivity reactions, loss of drug effect, renal impairment, neurocognitive disorders, and inhibitor development), AEs, serious adverse events (SAEs), and adverse reactions (ARs). • Evaluate joint health (Hemophilia Joint Health Score [HJHS]). • Collect information on affected joints at baseline and in the study. • Assess hemostasis during surgeries during the study. • Collect and evaluate patient-reported outcomes such as Hemophilia Treatment Satisfaction Questionnaire for adults (Hemo-SAT A), Hemophilia Quality of Life Measure for adults (Hemo-QoL-A), Hemophilia Quality of Life short form for children (Hemo-QoL-SF) and Work Productivity and Activity Impairment Scale (WPAI [+ CIQ: HS]).
Study design	Multinational, open-label, prospective, non-interventional, multicenter, cohort study. Each patient enrolled will be followed for 36 months (with the potential for further extension).

Population	Previously treated patients with hemophilia A receiving damoctocog alfa pegol with any kind of treatment modality (on-demand, prophylaxis, or intermittent prophylaxis), will be eligible to be enrolled into the study.
Variables	The variables for primary endpoint are: • Annualized number of reported total bleeds. • Severity of hemophilia • Severity of patient bleeding profile • Prophylaxis regimen • Time on treatment (i.e., damoctocog alfa pegolnaive- or not) • Disease characteristics • Age. The variables for secondary endpoints are: • Occurrence, duration, treatment, severity, and outcome of AEs, SAEs, and ARs (including AEs of special interest [hypersensitivity reactions, loss of drug effect, renal impairment, neurocognitive disorders, and inhibitor development]). • Number of reported total, spontaneous, joint, and trauma bleeds. • Retrospective and prospective location and number of affected joints. • Joint health measured by HJHS. • Newly affected joints (number and location). • Reported bleeds (number, type, location) during study and to 12 months prior to start of therapy with damoctocog alfa pegol. • Number of infusions and FVIII consumption to achieve hemostasis during surgery • Treatment satisfaction measured by Hemo-SAT A and Hemo-QoL (A and SF). • Work productivity and activity impairment measured by WPAI [+ CIQ: HS].
Data sources	Historic data are based on medical records or on information provided by the patient during routine clinical visits. Treatment-related data are documented during visits that take place in routine practice. The patient documents bleeding events and all other events that require infusions in a patient infusion diary. Validated patient questionnaires (Hemo-SAT A, Hemo-QoL [A and SF] and WPAI [+ CIQ: HS]) are used as sources for the

	patient assessment on satisfaction and treatment adherence. The HJHS is used as source for joint health status. The HEAD-US score is used as source for joint health status of patients with hemophilic arthropathy.
Study size	The study aims to enroll at least 200 patients.
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, minimum, median, quartiles, and maximum). Continuous variables will be described by absolute value and as change from baseline per analysis time point, if applicable. It is planned to have an annual interim analysis of baseline characteristics starting 1 year after the First Patient First Visit, and further annual analyses are planned on prospective treatment outcomes. For the primary analysis summary statistics of the number of total reported bleeds will be presented. ABRs will be calculated as the number of bleeding events divided by the length (in years) of the treatment regimen. ABRs will be characterized using descriptive statistics by calculating mean (± standard deviation), median, minimum, and maximum.
Milestones	First patient first visit: Q2 2019 Last patient first visit: Q2 2022 Last patient last visit: Q2 2025 Final report: Q1 2026

5. Amendments

Table 1: Amendments

Amendment number	Reason for amendment	New version number	Effective date
AM01	The global HEM-POWR protocol has been revised to comply with Japanese regulations.	v 1.1_JP	18 MAR 2019

	The amendment was generated as proof of written-based study design specific in Japan and will be reviewed by the Japanese regulatory authority (PMDA). To avoid redundant description or any conflict, the local Japanese amendment only focuses on critical information for PMDA communication (e.g., number of patients, observation period, timing of interim/final analysis, etc.).		

6. Milestones

Table 2 presents 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 enrollment 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 a stand-alone document (see Table 6) that is available upon request.

Table 2: Milestones

Milestone	Planned date
Start of data collection (First Patient First Visit)	Q2 2019
First interim analysis	1 year after FPFV
Second interim analysis	2 years after FPFV
End of data collection (Last Patient Last Visit)	Q2 2025
Registration in the EU PAS register	Q2 2019
Database clean	Q3 2025
Final statistical analysis	Q4 2025
Final report of study results	Q1 2026

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 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 inhabitants [1],[2]. All races and economic groups are affected equally [1]. Prevalence estimates vary by country, ranging between 5 and 21 cases per 100,000 male inhabitants. 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 2 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 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 [2].

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 is intended for prophylaxis and treatment of bleeds in previously treated patients (PTPs) with hemophilia A aged ≥12 years, with a weekly 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 was 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 effectiveness and long term safety of damoctocog alfa pegol drug usage. Detailed information will be collected on reported adverse events (AEs) of interest. These include loss of drug efficacy, hypersensitivity, renal impairment, and neurocognitive disorders. The AEs of hypersensitivity and loss of efficacy 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. 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 accumulation of PEG in plasma and tissues relative to some other PEGylated products. The pre-clinical 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.

These results can be used to educate patients, payors and providers about real-world prophylaxis dosing regimens with damoctocog alfa pegol.

Patients participating in HEMPOWR will be offered to enroll into a sub-study arm evaluating activity with an activity tracking device (ActiGraph; patient will be blinded to the activity tracking device values). The objective of the sub-study is to investigate relationship between patient daily regular activity and efficacy parameters collected from HEM-POWR.

Enrollment into HEM-POWR is not influenced by the patient's decision whether to participate in the sub-study or not. Participation in the sub-study is fully voluntary and will not impact the main objectives or data collected in HEM-POWR. Details of the sub-study, including the analysis of the activity data will be described in a separate sub-study protocol as a part of the main study.

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 [2],[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 [8]. In the phase II/III PROTECT VIII study [9], median annualized bleeding rate (ABR) was 2.1 for patients using damoctocog alfa pegol twice weekly, every 5 days, and every 7 days [9], and 1.5 during the long-term extension study. 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, there are currently no data regarding real-world use of the product outside of the clinical study.

8. Research questions and objectives

8.1 Primary objective

The primary objective in this study is:

- To assess the effectiveness of prophylaxis with damoctocog alfa pegol in the real-world setting through the collection of total bleeding events and analysis of ABR in the different prophylaxis regimens (following approved local label), or any other regimen prescribed by the physician as part of normal clinical practice) in patients with hemophilia A.

8.2 Secondary objectives

The secondary objectives in this study are to:

- Assess the long term safety of prophylaxis with damoctocog alfa pegol in the real-world setting through the collection and analysis of adverse events (AEs) of special interest (hypersensitivity reactions, loss of drug effect, renal impairment, neurocognitive disorders,

and inhibitor development), AEs, serious adverse events (SAEs), and adverse reactions (ARs).

- Evaluate joint health (Hemophilia Joint Health Score [HJHS]).
- Collect information on affected joints at baseline and in the study.
- Assess hemostasis during surgeries during the study.
- Collect and evaluate patient-reported outcomes such as Hemophilia Treatment Satisfaction Questionnaire for adults (Hemo-SAT A), Hemophilia Quality of Life Measure for adults (Hemo-QoL-A), Hemophilia Quality of Life short form for children (Hemo-QoL-SF) and Work Productivity and Activity Impairment Scale (WPAI [+ CIQ: HS]).

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 with any kind of treatment modality (on-demand, prophylaxis, or intermittent prophylaxis). The study is planned be conducted in multiple countries depending on timing of regulatory approval and national reimbursement access.

Prospective data will include prophylaxis regimen effectiveness measured by the number of ABR (reported in patient infusion diaries or documented by physicians, if patient infusion diary is not available), drug usage (IU/kg/infusion, IU/kg/year, and IU/kg/event), regimens used, patient-reported outcome (PRO) measurements (where applicable), such as validated, disease-specific and generic quality of life questionnaires and treatment satisfaction; as well as PK parameters (when available), joint outcomes (HJHS), and safety including AEs of special interest (hypersensitivity reactions, loss of drug effect, renal impairment, neurocognitive disorders, and inhibitor development) and drug-related ARs in standard clinical practice. Retrospective data will include documentation of previous therapy, lifetime duration on prophylaxis, medical condition, PK parameters (when available), and bleeds up to 12 months prior to use of damoctocog alfa pegol, in order to allow a stratification of patients by patient bleeding profile and disease characteristics (See Section 9.3.7).

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 patients planned observation period will be 36 months (with the potential for further extension), for the collection of long-term safety data and continuous prospective monitoring of joint health status over time.

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 occurs continuously throughout the 3 year observational period, i.e. each visit or assessment is to be documented in the eCRF/EDC system. Final data collection should be no sooner than 36 months after the initial visit.

For that reason the data documentation period will continue up to 3 months post Month 36 for the final follow-up time point.

Allocation of a visit or assessment to a specific follow-up time point (e.g. Month 12, 24 and 36, after initial visit) will be done during statistical analysis and will further be described in the Statistical Analysis Plan (SAP).

Interim analyses will be conducted yearly, starting 1 year after FPFV. Interim analyses include analysis of baseline characteristics, prospective treatment outcomes to produce annual safety reports and to provide preliminary results for publications.

9.1.1 Primary endpoint

The primary endpoint is:

- Mean/median annualized number of reported total bleeds in patients with hemophilia A,

9.1.2 Secondary endpoints

The secondary endpoints are:

- Occurrence, duration, treatment, severity, and outcome of AEs of special interest (hypersensitivity reactions, loss of drug effect, renal impairment, neurocognitive disorders, and inhibitor development), AEs, SAEs, and ARs.
- Hemostasis during surgery measured by number of infusions and consumption of FVIII product
- Change in joint scores (HJHS) from baseline to 12 months, to 24 months, to 36 months.
- Joint status evaluation by ultrasound (HEAD-US score), if available or part of standard clinical practice.
- Number of affected joints by patient, and the change from baseline to 12 months, to 24 months and to 36 months.
- Annualized number of spontaneous, joint, and trauma bleeds.
- Number of reported bleeds (total, spontaneous, joint, and trauma) during the study compared with number of reported bleeds (total, spontaneous, joint, and trauma) for previous FVIII products in the 12 months prior to enrollment into the study.
- Proportion of patients with 0 bleeds, and the difference in proportion comparing to previous prophylaxis treatment.
- Description of PK parameters for previous FVIII products versus damoctocog alfa pegol (if available in routine clinical practice).
- Efficacy of treatment of break-through bleeds.
- Change from baseline to 12 months, to 24 months and to 36 months in treatment satisfaction (Hemo-SAT A score).
- Change from baseline to 12 months, to 24 months and to 36 months in treatment satisfaction (Hemo-QoL [A and SF] score).

- Change from baseline to 12 months, to 24 months and to 36 months in work productivity and activity impairment (WPAI score).

9.2 Setting

9.2.1 Eligibility

All PTPs with hemophilia A receiving damoctocog alfa pegol with any kind of treatment modality (on-demand, prophylaxis, or intermittent prophylaxis), will be eligible to be enrolled into the study. Indications and contra-indications according to the local market authorization should be carefully considered.

9.2.2 Eligibility criteria

9.2.2.1 Inclusion criteria

- Diagnosis of hemophilia A.
- Patients previously treated for Hemophilia A.
- Patients without previous history of inhibitors or patients with previous history of inhibitors on standard prophylaxis therapy for at least 1 year prior to study entry.
- No current evidence* of FVIII inhibitor or clinical suspicion** of FVIII inhibitor.

  * Evidence of FVIII inhibitor as measured by the Nijmegen-modified Bethesda assay [<0.6 Bethesda units (BU/mL)] or Bethesda assay [<1.0 BU/mL] in 2 on consecutives samples.

  ** Documented or clinical suspicion of shortened FVIII half-life (<6 hours).
- Initiation of or currently on damoctocog alfa pegol with any kind of treatment modality (on-demand, prophylaxis, or intermittent prophylaxis).
- Signed informed consent/assent.

9.2.2.2 Exclusion criteria

- Concurrent participation in an investigational program with interventions outside of routine clinical practice.
- Diagnosis of any other bleeding/coagulation disorder other than hemophilia A.
- Contra-indications according to the local marketing authorization.
- Patient on immune tolerance induction (ITI) treatment at the time of enrollment.

9.2.3 Rationale for specific exclusion criteria

Patients with diagnosis of any other bleeding/coagulation disorder other than hemophilia A, contra-indications according to the local marketing authorization (including patients who have history of hypersensitivity reactions to the active substance, mouse or hamster protein, or other constituents of the product and patients with active FVIII inhibitors), and patients on ITI treatment will not be included according to the labeled indication and contra-indications, as a positive benefit-risk has not been established for these patient populations.

9.2.4 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.

9.2.5 Replacement

Patients will not be replaced after dropout.

9.2.6 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 damoctocog alfa pegol with any kind of treatment modality (on-demand, prophylaxis, or intermittent prophylaxis). Prophylaxis therapy is the recommended standard of care for patients with severe disease and those with moderate disease with severe patient bleeding profile. By enrolling eligible patients with mild, moderate, or severe disease, the study will be representative of real-world.

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 inhabitants, 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.

The patients documented in the study should be selected based only on eligibility according to a minimal set of selection criteria (see Sections 9.2.2 and 9.2.3). 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 as to whom to 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 in the Electronic Data Capture [EDC] system) will be used by each site to document also 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.).

The sample of study sites should, ideally, reflect the distribution of hemophilia A treatment settings in each participating country in the background of the specific local health system. Nevertheless,

the final sample of study sites will strongly depend on the willingness of physicians to participate in the study.

9.2.7 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, the study protocol does not define exact referral dates for those visits. After the initial visit, data collection will continue for 36 months (with the potential to be extended). Data collection occurs continuously throughout the observational period, i.e. each visit or assessment is to be documented in the eCRF/EDC system. Typical information to be collected are summarized in Table 3.

Enrollment/Initial visit

Once a patient is found to be eligible for inclusion, the physician will inform the patient and legal representative (where applicable) about the study. This will include discussing the informed consent/assent form and asking the patient/legal representative to read and - upon agreeing to participate - sign the informed consent/assent form (see Section 10.4).

Baseline information is recorded with the status at the initial visit before the first drug administration after enrollment into the study.

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 occurs continuously throughout the 3 year observational period, i.e. each visit or assessment is to be documented in the eCRF/EDC system. Final data collection should be no sooner than 36 months after the initial visit. For that reason the data documentation period will continue up to 3 months post Month 36 for the final follow-up timepoint.

Allocation of a visit or assessment to a specific follow-up timepoint (e.g. Month 12, 24 and 36 after initial visit) will be done during statistical analysis and will further be described in the Statistical Analysis Plan (SAP).

In case a patient is seen by more than 1 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.

End of observation and final safety follow-up

The final data collection (end of observation) should be no sooner than 36 months after initiation of the observational period, except where the study initiator decides to extend the study, or where documentation is no longer possible, such as where the patient/legal representative withdraws consent, is lost to follow-up, death, switch to other therapy (permanently stop damoctocog alfa pegol), or the decision to terminate the study.

A final safety follow-up (collection of AEs) will be up to 30 days after receiving the last therapy within the study period.

Lost to follow-up

A patient is regarded as 'Lost to follow-up' in case no further information can be expected from the patient at a given point in time.

In case no information was obtained from a patient within 24 month since the last data collection time point the site personnel is requested to apply due diligence – within the applicable legal limits – to contact patients to ascertain the reason. In case no information can be retrieved, the site should confirm that the patient is lost to follow-up and document the end of observation.

Table 3: Tabulated overview on data collected during the study

	Enrollment/ Initial visit	**Follow up visit (including end of observation)**
Eligibility Assessment (see 9.2.2)	X	
Date	X	X
Demographic data (see 9.3.3)	X	
General medical/surgical history (see 9.3.5)	X	
Disease history (see 9.3.4)	X	
Bleed history (see 9.3.1)	X	
Prior FVIII treatment history (see 9.3.4)	X	
Damoctocog alfa pegol history (if any, see 9.3.7)	X	
Current prescribed damoctocog alfa pegol regimen (see 9.3.7)	X	X
Damoctocog alfa pegol dose/regimen changes, treatment switches (see 9.3.7)		X (Continuous collection)
Patient-Reported Data (Hemo-SAT A, Hemo-QoL-A, Hemo-QoL Short Form, WPAI [+ CIQ: HS]; see 9.3.10)	X	X (Month 12, 24, 36)

	Enrollment/ Initial visit	Follow up visit (including end of observation)
Physical examination (weight, height, vital signs)[1]	X	X
Joint Health (HJHS)	X	X
Ultrasound data[1]	X	X
Affected joints	X	X
Damoctocog alfa pegol Pharmacokinetic analysis[1,2] (see 9.3.7)	X	X
Concomitant medication (see 9.3.6)	X	X
Adverse events (includes systematically collected AEs and AEs of special interest (see 11))[3]	X (Continuous collection)	
Inhibitor[1]	X	X
Patient infusion diary		X (Continuous collection)
Physician recorded bleeds[4]		X (Continuous collection)
Physician recorded surgeries		X (Continuous collection)
Reason for end of observation (see 9.3.11)		X (once, at occurrence)

[1] Routine examinations only, if available.

[2] PK analysis is at physician's discretion. PK testing (and the frequency of testing per the table) is part of the routine use of the product.

[3] Adverse events (up to 30 days after the last treatment with damoctocog alfa pegol in study period).

[4] Serious, life-threatening bleeds and surgery bleeds to be recorded by the physician. Physician to ask patient at each visit regarding bleeds.

9.3 Variables

The physician collects historical study-relevant data (demographic and clinical characteristics) from medical records if available (or else by interviewing the patient at the initial [baseline] visit) and treatment-related data during visits occurring within pre-defined data collection periods (see section 9.2.7). The physician documents the study-relevant data for each patient in the eCRF/EDC system. The CRF is kept as a stand-alone document (see Table 6) and is available upon request.

9.3.1 Variables to determine the primary endpoint

The variables for primary endpoint are:

- Annualized number of reported total bleeds.
- Severity of hemophilia.
- Severity of patient bleeding profile.
- Disease characteristics
- Prophylaxis regimen.
- Age.
- Previous exposure to damoctocog alfa pegol (i.e. naïve vs. non-naïve).

9.3.2 Variables to determine the secondary endpoints

The variables for secondary endpoints are:

- Safety:
    - Occurrence, duration, treatment, severity, and outcome of AEs, SAEs, and ARs (including AEs of special interest [hypersensitivity reactions, loss of drug effect, renal impairment, neurocognitive disorders, and inhibitor development]).
- Effectiveness:
    - Number of reported total, spontaneous, joint, and trauma bleeds.
    - Retrospective (diagnosed clinically, by imaging, by the patient, or by the physician) and prospective location and number of affected joints.
    - Joint health measured by HJHS.
    - Newly affected joints (number and location).
    - Reported bleeds (number, type, location) during study and up to 12 months prior to start of therapy with damoctocog alfa pegol. Prior bleeds to be estimated by the patient and the physician. Reported bleeds during the study will be recorded in the patient infusion diary and serious, life-threatening bleeds and surgery bleeds will be documented by the physician.
    - Number of infusions and FVIII consumption to achieve hemostasis during surgery.
    - Patient-report outcome:
        - Treatment satisfaction measured by Hemo-SAT A.
        - Health-related quality of life measure by Hemo-QoL (A and SF).
        - Work productivity and activity impairment measured by WPAI [+ CIQ: HS].

9.3.3 Demography

For demographic/socio-demographic assessment, the following data will be recorded:

- Year of birth.

- Age.
- Sex.
- Race (e.g., Asian, Black, White, not reported) (only where legally permitted).
- Ethnic origin (e.g., not Hispanic or Latino, Hispanic or Latino, not reported) (only where legally permitted).
- Body weight, height, body mass index, and vital signs (routine assessments only).

9.3.4 Hemophilia Disease history

Disease history describes any medical findings that are relevant to the underlying disease and were present before enrollment into the study. Findings and diagnoses meeting the criteria listed below have to be documented, if available:

- Date of diagnosis (at least the year).
- Type of gene mutation, if available.
- Family history of hemophilia.
- Family history of inhibitors.
- Severity of hemophilia at initial diagnosis.
- Age/age group at first treatment with factor FVIII replacement therapy.
- Age at initiation of prophylaxis therapy, if applicable.
- Duration of prophylaxis treatment lifetime.
- Patient history of inhibitors (date, high/low titer, etc.).
- ITI history.
- Most recent FVIII product (name, treatment modality [on-demand, prophylaxis, or intermittent prophylaxis], dose/regimen) up to 12 months prior to start of therapy with damoctocog alfa pegol.
- PK parameters from most recent FVIII products, if available.
- Number and location of affected joints.
- Reported previous bleeds (number, type, and location) within 12 months prior to start of therapy with damoctocog alfa pegol.
- Ultrasound scanning (Hemophilia Early Arthropathy Detection with Ultrasound [HEAD-US]) to evaluate joints of patients with hemophilic arthropathy [28].

9.3.5 Co-morbidity (medical history and concomitant diseases)

Co-morbidities are any medical findings, as they pertain to the study indication, that were present up to 12 months prior to start of therapy with damoctocog alfa pegol, independent of whether or not they are still present. They have to be documented under medical history/concomitant diseases, if available.

Findings meeting the criteria listed below are considered to be relevant to the study indication and have to be documented, if available:

- Human immunodeficiency virus.
- Hepatitis C virus (full serology).
- Hepatitis B virus (full serology).
- Liver disease.
- Hypertension.
- Chronic arthropathy (i.e., not hemophilic arthropathy).
- Chronic pain.
- Renal disease.
- Neurocognitive disorders.
- Neurological disorders.
- Previous hypersensitivity to FVIII administration.

9.3.6 Prior and concomitant medication/treatments

Medication taken /treatment received prior to study start (initiated and stopped before study start) is termed prior medication/treatment. Prior medication/treatment for hemophilia A at inclusion (on-demand, prophylaxis, or intermittent prophylaxis) received up to 12 months prior to study enrollment or initiation of damoctocog alfa pegol, whichever comes earlier are considered to be relevant to the study indication and have to be documented, if available.

All medication taken/treatment received (either initiated before study start or during the study) in addition to damoctocog alfa pegol for any indication is termed concomitant medication/treatment and has to be documented, if available.

9.3.7 Exposure/treatment

During the study, damoctocog alfa pegol exposure/treatment data will be collected by the physician, including but not limited to:

- Date of first and last dose during the study.
- Exposure days previous treatment.
- Damoctocog alfa pegol exposure days.
- Date of damoctocog alfa pegol treatment start.
- Date of first and last dose before enrollment (if applicable).
- Prescribed dose of damoctocog alfa pegol.
- Prescribed regimen of damoctocog alfa pegol.
- Reason for any dose and/or regimen change
- Number of infusions and by-product FVIII consumption (for overall, prophylaxis, bleeds, and other events)
- Reason for selection of dose/regimen at baseline (first visit). Physician to choose and rank in order of importance the top 3 reasons from predefined list (see Annex 3).

- PK parameters from damoctocog alfa pegol (Half-life [t½], FVIII trough, FVIII peak levels, in-vivo recovery), if available.
- Any surgery requiring an infusion, is also documented, including the following information:
    - Date of treatment.
    - Type of surgery (major or minor; see Annex 4), if applicable.
    - Number of infusions.
    - Dose (IU) per infusion/bolus infusion/other for each event/surgery (if applicable).
    - Total bleeding volume (mL) during surgery.
    - Blood transfusions (red blood cells, platelets, etc.) and total volume (mL).

For data collected by the patient/legal representative (where applicable), a diary will be used as source:

- Patient infusion diary. All bleeding events are documented, including:
    - Date of bleeding event.
    - All data referent to prophylaxis infusions.
    - Reason for infusion and location of bleed.
    - Date of treatment.
    - Number of infusions and dose per infusion for each bleeding event.

9.3.8 Inhibitor measurement

Data documented by the physician, if collected, include:

- Date of measurement.
- Inhibitor test result (negative/positive).
- Titer of inhibitor (Bethesda units).

9.3.9 Exploratory Assessment (PEG measurement)

Data on PEG measurements will be recorded if it is part of the routine practice.

9.3.10 Patient-reported outcomes

The questionnaires (Hemo-SAT A, Hemo-QoL [A and SF] and WPAI [+ CIQ: HS]) and patient infusion diary will be completed by the patient/legal representative, where applicable.

Patients/legal representatives will be requested to complete the questionnaires during their routinely scheduled visits at the study site.

9.3.11 End of observation

If available, the date and the primary reason for end of observation/study discontinuation should be stated.

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.

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 1 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.

The HJHS is used as source for joint health status. The HEAD-US score is used as source for joint health status of patients with hemophilic arthropathy.

Validated patient questionnaires (Hemo-SAT A, Hemo-QoL [A and SF] and WPAI [+ CIQ: HS]) are used as sources for the patient assessment on satisfaction and treatment adherence. Patients/legal representatives will be requested to complete the questionnaires during their routinely scheduled visits at the study site.

Hemophilia Treatment Satisfaction Questionnaire (Hemo-SAT)

This is a hemophilia-specific treatment satisfaction questionnaire. The Hemo-SAT questionnaire version for adults (Hemo-SAT A) consists of 34 items pertaining to 6 dimensions (Ease & Convenience, Efficacy, Burden, Specialist/Nurses, Center/Hospital, General Satisfaction). The Hemo-SAT A questionnaire is suitable for adult patients and adolescents (>12 years of age) and should be completed at the initial (baseline) visit, at Month 12, Month 24 and Month 36.

Hemophilia Quality of Life Measure for Adults (Hemo-QoL-A) and Hemo-QoL Short Form (Hemo-QoL-SF) for Children and Adolescents

The questionnaire is used to capture the full impact of damoctocog alfa pegol and the treatment modalities on the patients' hemophilia-specific quality of life. Hemo-QoL-A is a hemophilia-specific quality of life questionnaire for adults aged 18 years and above. The questionnaire has 41 items covering 6 domains: Physical Functioning, Role Functioning, Worry, Consequences of Bleeding, Emotional Impact, and Treatment Concerns. For patients younger than 18 years, the Hemo-QoL-SF Questionnaire for children and adolescents (12 to 17 years) is used. The Hemo-QoL-SF contains 35 questions covering 9 domains: Physical Health, View of Yourself, Family, Friends, Others, Sports, Dealing, and Treatment. The respondent burden for both questionnaires is approximately 15 minutes. Patients should complete the Hemo-QoL (A or SF) questionnaire at the initial (baseline) visit, at Month 12, Month 24 and Month 36.

Work Productivity and Activity Impairment Scale (WPAI)

The study will include the Work Productivity and Activity Impairment: Hemophilia Specific (HS) questionnaire also containing classroom impairment questions (CIQ) (WPAI [+ CIQ: HS]).

The WPAI questionnaire has been widely used in PRO work since its initial development over 20 years ago. There have been approximately 40 validation studies regarding the use of this tool in various chronic disease states, as well as for general health. In addition to the validation studies, there are documented uses of the tool in various chronic conditions including hemophilia. A hemophilia specific questionnaire is also available and translated in many languages. It has been recently used in several studies [29].

The WPAI [+ CIQ: HS] assesses the effect of hemophilia on ability to work, attend classes, and perform regular daily activities in ages 12 and above. The questionnaire is self-administered and comprises nine questions that elicit information on work, classroom, and daily activity impairment during the previous seven days. Scores are expressed as percentages of impairment/ productivity loss, with higher scores indicating greater impairment. The respondent burden for this questionnaire is approximately 10 minutes. The assessment should be performed at the initial (baseline) visit, at Month 12, Month 24 and Month 36.

9.5 Study size

The study aims to enroll at least 200 patients. Assuming a dropout rate of 10%, 180 patients will be available for the effectiveness analysis. Based on this sample size, the primary endpoint (total ABR in moderate and severe patients who receive prophylactic damoctocog alfa pegol treatment) can be estimated with reasonably good precision.

It is a standard to assume that ABR follows a negative binomial distribution NB(μ, θ), where μ is the mean ABR of prophylaxis regimen, and θ is the dispersion parameter for variance. Previously, the PROTECT study [9] showed an ABR on prophylaxis of 4, with 95% confidence interval (CI) of 3 to 5 per person, and a dispersion parameter of 1. A simulation study shows, if it is conservatively assumed μ=6, θ=1, the half width of 95% CI for mean ABR in the prophylactic population (assuming n=180) is no larger than 0.96 with a probability of 0.9. For the subsequent subgroup analysis, precision of mean-ABR estimates depends on the size of each subgroup. Estimated 95% CIs in various scenarios are summarized in Table 4.

Table 4: Estimated 95% confidence intervals in various scenarios

Number of patient	95% CI	Precision based on half width of the 95% CI
36	(4.32, 8.66)	± 2.17
108	(4.92, 7.39)	± 1.23
180	(5.16, 7.07)	± 0.96

Sample size justification is further based on the need to observe a rare AE, and it is reasonable to assume that the number of patients in the safety analysis set (SAF) is close to the target enrollment (i.e., at least 200).

Table 5 presents the expected probabilities of observing a specific number of patients with events in the study under varying underlying incidence risks. The table indicates that 200 patients will provide an adequate chance of observing events with event rate larger than 2.0%, as there is a 76.5% chance of observing at least 3.

Table 5: Probability of observing patients with events with increasing sample size

Number of patients	**Observed patients with events (*x*)**	**Probability(%) of observing at least *x* patients**			
		Underlying percentage of patients with events			
		0.5%	1.0%	1.5%	2.0%
100	at least 1	0.394	0.634	0.779	0.867
	at least 3	0.014	0.079	0.190	0.323
200	at least 1	0.633	0.866	0.951	0.982
	at least 3	0.080	0.323	0.579	0.765

9.6 Data management

Patient-reported data on bleeds and infusions will be documented in a patient diary. Physicians document the study-relevant data for each patient in the eCRF. The CRF is available upon request (see Table 6).

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 6). 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 6).

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.

Statistical analysis of the HEM-POWR sub-study will be mostly of exploratory nature, descriptive statistics can also be applied, and will be in the statistical section of the sub-study protocol.

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). Separate analyses for individual participating countries or regions will be provided if required for local reasons when sufficient data is available.

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
- Prior FVII treatment

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
- Surgeries
- Adverse events

Annual analyses are planned to provide annual safety reports and preliminary results to support publications. The final analysis will be performed after 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 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 is available upon request (see Table 6).

Analysis populations:

Patients who took at least 1 dose of damoctocog alfa pegol in the study will be eligible for safety analysis. The full analysis set (FAS) will include all SAF patients who have data on infusions and or bleeding events available. This will include patients who were not followed-up for 3 complete years of prophylaxis. PK analyses will be performed on the PK analysis set. The PK analysis set includes all SAF patients who have evaluable PK data.

Sub-populations:

Data will be stratified by prophylaxis dosing regimen (following approved local label, see Section 9.7.3), severity of hemophilia (mild, moderate, or severe), severity of patient bleeding profile at baseline (ABR in the last 12 months prior to enrollment), medical history (in particular joint status [affected joint: yes/no; 1 affected joint/>1 affected joint]), age groups, and time on treatment (i.e., damoctocog alfa pegol-naive or not). The prophylaxis-dosing regimen as prescribed by the physician at the beginning of the study will be used for stratification, unless otherwise stated.

Assignment of patients into treatment categories in case of changes to the regimen or switch to on-demand will be specified within SAP. Whenever reasonable, further subgroups (e.g., sex, baseline patient/disease/pre-treatment characteristics) will be specified in the SAP. Selected tables (including safety events, treatment administration and prophylaxis regimen) will be presented by history of inhibitors and exposure days (to FVIII product) at baseline.

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.
- Impute missing exposure and AE/concomitant medication start and/or end date based on a "worst case" scenario.
- In cases when imputation is necessary, reasons for missing data will be identified (such as: due to loss to follow-up, skip question patterns in the eCRF, or random data collection issues) and appropriate methods of analysis (such as last-observation-carried-forward, impute to the mean, maximum likelihood, and multiple imputation) will be selected based on reasonable assumptions.

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 clinical study reports.

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 person-years denominator when estimating rates of safety outcomes for prophylactic damoctocog alfa pegol.

Confounders and effect-modifying factors:

Because of the non-interventional character of the study, results may be subject to bias and confounding. Multiple regression and stratified analysis will be used in this study to control for differences between groups.

Influencing factors such as treatment regimen, severity of hemophilia, patient bleeding profiles, sex, time on treatment, and age groups will be used as the basis for defining sub-populations for the main analysis.

Covariates included in the study are those determined to be risk factors for a given outcome of interest or predictors of exposure, such as medical histories, pre-treatment history, and country. Covariates will be determined at baseline and be used for regression model development. Detailed methodologies and analysis process will be documented in the SAP.

9.7.2 Analysis of demography, disease details, prior and concomitant medication/treatment, and other baseline data

Demographics and baseline disease characteristics will be described by frequency tables or summary statistics. Baseline disease characteristics will include the most recent FVIII product used prior to the start of damoctocog alfa pegol treatment. Some continuous variables will be categorized and presented in frequency tables in addition to summary statistics. Categories will be defined in the SAP.

Number of bleeds prior to enrollment (or first administration of the study drug, for damoctocog alfa pegol non-naïve patients) into the study will be summarized.

Prior and concomitant medication/treatment and medical history will be presented by frequency tables or summary statistics.

9.7.3 Analysis of treatment exposure

Analysis of treatment exposure will be performed on the SAF.

In this study, the following 4 types of exposure based on physician's prescription will be considered:

- Prophylaxis: twice weekly (including any prescription more than 7 times per month).
- Prophylaxis: every 5 days (including any prescription between >5-7 times per month).
- Other: if not listed above.
- All.

The damoctocog alfa pegol exposure will start with the first infusion in the study. The period of continuous exposure per treatment pattern (following approved local label), stops whenever prescribed damoctocog alfa pegol treatment regimen changes. Treatment patterns for non-naïve patients will also be summarized.

Exposure duration (in days) will be analyzed descriptively by summary statistics and frequency tables per treatment pattern.

9.7.4 Analysis of effectiveness variable

Analysis of the primary outcome will be performed on the FAS, and if needed and data permits, within the subgroups defined in Section 9.7.1.

ABR:

Summary statistics of the number, type, location, and severity of reported bleeds (total, spontaneous, joint, and trauma) will be presented.

The primary analysis on ABR will be performed in patients receiving prophylactic treatment. ABRs will first be characterized using descriptive statistics by calculating mean (± standard deviation [SD]), median, minimum, and maximum. Further, the mean ABRs along with 95% CIs will be estimated using a negative binomial regression model corrected for over-dispersion, and with relevant treatment and disease characteristics as covariates and observed prophylactic treatment period as an offset variable.

When enough data is collected, additional analyses include: 1) comparing the ABR in patients receiving prophylactic treatment with those who are not treated with standard prophylaxis; 2) comparing the ABR in patients receiving damoctocog alfa pegol prophylactic treatment with the ABR prior to the damoctocog alfa pegol treatment.

Further details of the analysis will be described in the SAP.

Patients with 0 bleeding events:

The proportions of bleed-free patients and 95% CIs for the proportions will be presented.

Surgeries and Hemostasis during Surgeries :

Frequencies of type and classification of surgeries, number of patients having had surgeries, FVIII treatment other than damoctocog alfa pegol (product, number of infusions, consumptions) used during surgeries, as well as hemostasis (number of infusions, FVIII consumptions) will be summarized descriptively.

Affected joints:

Number and location of affected joints will be summarized descriptively. Change from baseline will be evaluated at end of the study for affected joints.

Joint health:

Joint health will be assessed by HJHS and summarized descriptively. Change from baseline will be evaluated at end of the study for HJHS.

Joint ultrasonography results will be done for index joints per standard clinical practice using HEAD-US methods [28]. HEAD-US scores will be summarized descriptively.

PRO:

See Section 9.7.6.

9.7.5 Analysis of drug utilization variables

Analysis of the drug utilization will be performed on the FAS, and if needed and data permits, within the subgroups defined in Section 9.7.1.

Treatment pattern:

Summary statistics for the prescribed treatment regimen will be provided every 12 months. The proportions of patients per treatment regimen and 95% CIs for the proportions will be presented. A shift table or diagram will be provided to present the change from baseline regimens.

The physician's determinants for initial choice of a treatment regimen will be provided in frequency tables. Changes in prescribed regimen to be evaluated with documentation in the patient diary and clinical record and reason for change will be summarized and presented using frequency tables.

Factor consumption:

Factor consumption will be analyzed descriptively based on the patient infusion diary, including the annualized number of infusions per patient, annualized total/average dose, and other infusion characteristics. Summary statistics and frequency tables will be provided per treatment pattern, treated bleeds, and other events (e.g., surgeries).

Sensitivity analyses will be performed in case of incomplete patient infusion diary.

9.7.6 Analysis of patient-reported outcomes

Analysis of PRO will be performed on the FAS, and if needed and data permits, subgroup analysis may be performed based on the subgroups defined in Section 9.7.1.

Appropriate scores for questionnaires will be derived and changes from baseline will be analyzed by summary statistics. Patients with improved, unchanged, and worsened scores will be presented using a shift table. Further details of the analysis will be described in the SAP.

9.7.7 Analysis of adverse events

The analysis described in this section will be performed on incident treatment-emergent adverse events (TEAEs) on the SAF.

An overview table displaying all TEAEs 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 outcome of death.
- Events leading to 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 TEAEs will be presented by primary System Organ Class (SOC) and Preferred Term (PT). AEs will primarily be classified by MedDRA PT. Aggregate incidences at the SOC level will 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.

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

9.7.8 Analysis of pharmacokinetics

Analysis of PK will be performed in the PK analysis set.

A frequency table will be provided for approaches to PK dosing, and if needed and data permits, subgroup analysis may be performed based on the subgroups defined in Section 9.7.1.

For the primary analysis, summary statistics (n, mean, SD, median, minimum, first quartile [Q1], third quartile [Q3], maximum, geometric mean, geometric SD, and coefficient of variation) will be displayed for PK measurement results.

If data permit, the difference in PK parameters of damoctocog alfa pegol and pre-treatment will be evaluated on a log scale.

Listings will be provided for all available PK measurements collected at baseline and during the study.

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 OS protocol and the eCRF.

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.

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. Operational measures which positively impact data quality will be considered as required. If such measures are used, the documentation can be made available upon request (see Table 6).

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 6).

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 6).

National and international data protection laws as well as regulations on OS 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]) [30]. 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 6).

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. In the second step source data verification will be conducted. The purpose is to review the documented data for completeness and plausibility, adherence to the OS protocol and verification with source documents.

Detailed measures for quality reviews will be described in the Quality Review Plan, which is available upon request (see Table 6).

9.8.3 Storage of records and archiving

Bayer 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 the study initiator and funder 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.

The sample size is not large enough to observe extremely rare AEs. 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 lost to follow-up). The bleeding event, treatment pattern, PROs, and the drug utility data collected in this study may suffer from bias due to measured and unmeasured confounders, selection bias, as well as reporting bias. Additionally, both drug utility and adherence to treatment is prone to be biased by adherence to documentation. Finally, it is acknowledged that channelling bias (confounding by indication) can be present in observational studies despite use of more advanced study designs and analytical methods. Because confounders or risk factors are specific for each outcome, adjusting for confounding for each outcome would require complete information of measured and unmeasured risk factors for each outcome associated with exposure to damoctocog alfa pegol.

The diversity of the data sources may add complexity as the implementation of standardized bleed/infusion diaries may be difficult as patients may continue to use their own diaries (paper, electronic, or software). In addition, the information may only be available by means of the physician documents.

9.10 Other aspects

Not applicable.

10. Protection of human subjects

10.1 Ethical conduct of the study

This study is an OS where damoctocog alfa pegol is prescribed in the 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 [31]). Recommendations given by other organizations will be followed as well (e.g., European Federation of Pharmaceutical Industries and Associations [EFPIA] [32], European Network of Centers in Pharmacoepidemiology and Pharmacovigilance [ENCePP] [33]).

In addition, the guidelines on Good Pharmacovigilance Practices (GVP module VI [34] and since the study qualifies as a Post-Authorization Safety Study (PASS), GVP module VIII [35],[36]) 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 the study initiator and funder. The IEC/IRB must supply to the study initiator and funder, 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 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 AG. If the patient name appears on any document, it must be obliterated before a copy of the document is supplied to Bayer 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 [37].

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 [1], occupational exposure, lack of drug effect, medication error, overdose, drug abuse, drug misuse or drug dependency itself, as well as any resulting event.

[1] 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).

- 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 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 surgical site).
- 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 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 the 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 precedent.

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 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 a 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 OS. 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 qualify 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 [34]) 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 AG within 24 hours 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

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. The events are captured in the assessment of effectiveness. However, if the bleed requires hospitalization, it must be reported as an SAE.

The physician will be asked to document in the eCRF whether the clinical site participates in any registries whereby AEs could be reported to both the registry and the HEM-POWR 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 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 OS 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 [38], Strengthening the Reporting of Observational Studies in Epidemiology [STROBE] [39]). No individual physician may publish the results of this study, or their own patients, without prior approval from the MAH.

13. References

1. National Hemophilia Foundation, [Online]. Available: https://www.hemophilia.org/About-Us/Fast-Facts. [Accessed 16 November 2017].
2. A. Srivastava, A. K. Brewer, E. P. Mauser-Bunschoten, N. S. Key, S. Kitchen, A. Llinas, C. A. Ludlam, J. N. Mahlangu, K. Mulder, M. C. Poon and A. Street, "Guidelines for the management of hemophilia," *Haemophilia*, vol. 19, no. 1, pp. e1-47, 2013.
3. World Federation of Hemophilia Guidelines for the Management of Hemophilia, 2012. [Online]. Available: https://www1.wfh.org/publication/files/pdf-1472.pdf. [Accessed 16 November 2017].
4. D. P. Agaliotis, R. A. Zaiden and S. Ozturk, Hemophilia A, 2009. [Online]. Available: https://www1.ededicine.medscape.com/article/210104-overview. [Accessed 16 November 2017].
5. H. C. Rossbach, "Review of antihemophilic factor injection for the routine prophylaxis of bleeding episodes and risk of joint damage in severe Hemophilia A," *Vasc Health Risk Manag*, vol. 6, pp. 59-68, 2010.
6. B. Mei, C. Pan, H. Jiang, H. Tjandra, J. Strauss, Y. Chen, T. Liu, X. Zhang, J. Severs, J. Newgren, J. Chen, J. M. Gu, B. Subramanyam, M. A. Fournel, G. F. Pierce and J. E. Murphy, "Rational design of a fully active, long-acting PEGylated factor VIII for hemophilia A treatment," *Blood*, vol. 116, no. 2, pp. 270-279, 2010.
7. S. Yegneswaran, X. Jiang and P. Yesantharao, "Site-directed PEGylation of BDD-FVIII (BAY 94-9027) does not alter the ability of the molecule to generate thrombin, activate FX, or become inactivated by aPC.," in *American Society of Hematology*, San Francisco, December 6-9, 2014.
8. T. E. Coyle, M. T. Reding, J. C. Lin, L. A. Michaels, A. Shah and J. Powell, "Phase I study of BAY 94-9027, a PEGylated B-domain-deleted recombinant factor VIII with an extended half-life, in subjects with hemophilia A," *J Thromb Heamost*, vol. 12, no. 4, pp. 488-496, 2014.
9. M. T. Reding, H. J. Ng, L. H. Poulsen, M. E. Eyster, I. Pabinger, H. J. Shin, R. Walsch, M. Lederman, M. Wang, M. Hardtke and L. A. Michaels, "Safety and Efficacy of BAY 94-9027, a prolonged-half-life factor VIII," *J Thromb Haemost*, vol. 15, no. 3, pp. 411-419, 2017.
10. E. Santagostino, K. Saxena, G. Kenet, K. Fischer, T. Biss, S. Radke and L. A. Michaels, "PROTECT VIII kids trial results: BAY 94-9027 safety and efficacy in previously treated children with severe hemophilia A," *Haemophilia*, vol. 22, no. (suppl 4), p. 41, 2016.
11. A. Gringeri, B. Lundin, S. von Mackensen, L. Mantovani, P. M. Mannucci and ESPRIT Study Group, "A randomized clinical trial of prophylaxis in children with hemophilia A (the ESPRIT) Study)," *J Thromb Haemost*, vol. 9, no. 4, pp. 700-710, 2011.
12. M. J. Manco-Johnson, T. C. Abshire, A. D. Shapiro, B. Riske, M. R. Hacker, R. Kilcoyne, J. D. Ingram, M. L. Manco-Johnson, S. Funk, L. Jacobson, L. A. Valentino, W. K. Hoots, G. R. Buchanan, D. DiMichele, M. Recht, D. Brown, C. Leissinger, S. Bleak, A. Cohen, P. Mathew, A. Matsunaga, D. Medeiros, D. Nugent, G. A. Thomas, A. A. Thompson, K.

McRedmond, J. M. Soucie, H. Austin and B. L. Evatt, "Prophylaxis versus episodic treatment to prevent joint disease in boys with severe hemophilia," *N Engl J Med*, vol. 357, no. 6, pp. 535-544, 2007.

13. M. J. Manco-Johnson, C. L. Kempton, M. T. Reding, T. Lissitchkov, S. Goranov, L. Gercheva, L. Rusen, M. Ghinea, V. Uscatescu, V. Rescia and W. Hong, "Randomized, controlled, parallel-group trial of routine prophylaxis vs. on-demand treatment with sucrose-formulated recombinant factor VIII in adults with severe hemophilia A (SPINART) [published correction appears in J Thromb Haemost. 2014;12:119-122]," *J Thromb Haemost*, vol. 11, no. 6, pp. 1119-1127, 2013.
14. K. Kavakli, R. Yang, L. Rusen, H. Beckman, D. Tseneklidou-Stoeter, M. Maas Enriquez and LEOPOLD II Study Investigators, "Prophylaxis vs. on-demand treatment with BAY 81-8973, a full-length plasma protein-free recombinant factor VIII product: results from a randomized trial (LEOPOLD II)," *J Thromb Haemost*, vol. 13, no. 3, pp. 360-369, 2015.
15. National Hemophilia Foundation, "Medical and Scientific Advisory Council (MASAC) recommendations concerning prohylaxis (regular administration of clotting factor concentrate to prevent bleeding)," Document #241, 2016.
16. S. Geraghty, T. Dunkley , C. Harrington, K. Lindvall, J. Maahs and J. Sek, "Practice patterns in haemophilia A therapy - global progress towards optimal care," *Haemophilia*, vol. 12, no. 1, pp. 75-81, 2006.
17. V. S. Blanchette, "Prophylaxis in the haemophilia population," *Haemophilia*, vol. 16, no. (suppl 5), pp. 181-188, 2010.
18. M. R. Hacker, S. Geraghty and M. Manco-Johnson, "Barriers to compliance with prophylaxis therapy in haemophilia," *Haemophilia*, vol. 7, no. 4, pp. 392-396, 2001.
19. A. Shapiro, "Development of long-acting recombinant FVIII and FIX Fc fusion proteins for the management of hemophilia," *Expert Opin Biol Ther*, vol. 13, no. 9, pp. 1287-1297, 2013.
20. P. Collins, V. S. Blanchette, K. Fischer, S. Björkman, M. Oh, S. Fritsch, P. Schroth, G. Spotts, J. Astermark, B. Ewenstein and r.-P. S. Group, "Break-through bleeding in relation to predicted factor VIII levels in patients receiving prohylactic treatment for severe hemophilia A," *J Thromb Haemost*, vol. 7, no. 3, pp. 413-420, 2009.
21. W. Kreuz, C. Escuriola-Ettingshausen, M. Funk, H. Schmidt and B. Kornhuber, "When should prophylactic treatment in patients with haemophila A and B start? - The German experience," *Haemophilia*, vol. 4, no. 4, pp. 413-417, 1998.
22. L. A. Valentino, "Blood-induced joint disease: the pathophysiology of hemophilic arthropathy," *J Thromb Haemost*, vol. 8, no. 9, pp. 1895-1902, 2010.
23. L. A. Valentino, V. Mamonov, A. Hellmann, D. V. Quon, A. Chybicka, P. Schroth, L. Patrone, W. Y. Wong and Prophylaxis Study Group, "A randomized comparison of two prophylaxis regimens and a paired comparison of on-demand and prophylaxis treatments in hemophilia A management," *J Thromb Haemost*, vol. 10, no. 3, pp. 359-367, 2012.
24. B. A. Konkle, O. Stasyshyn, P. Chowdary, D. H. Bevan, T. Mant, M. Shima, W. Engl, J. Dyck-Jones, M. Fuerlinger, L. Patrone , B. Ewenstein and B. Abbuehl, "Pegylated, full-

length, recombinant factor VIII for prophylactic and on-demand treatment of severe hemophilia A," *Blood*, vol. 126, no. 9, pp. 1078-1085, 2015.

25. S. R. Lentz, M. Misgav, M. Ozelo, S. Z. Salek, D. Veljkovic, M. Recht, M. Cergueira, A. Tiede, B. Brand, M. E. Mancuso, S. Seremetis, A. Lindblom and U. Martinowitz, "Results of a large multinational clinical trial (guardianTM 1) using prphylactic treatment with turoctocog alfa in adolescent and adult patients with severe haemophilia A: safety and efficacy," *Haemophilia*, vol. 19, no. 5, pp. 691-697, 2013.

26. J. Mahlangu, J. S. Powell, M. V. Ragni, P. Chowdary, N. C. Josephson, I. Pabinger, H. Hanabusa, N. Gupta, R. Kulkarni, P. Fogarty , D. Perry, A. Shapiro, K. J. Pasi, S. Apte, I. Nestorov, H. Jiang, S. Li, S. Neelakantan, L. M. Cristiano, J. Goyal, J. M. Sommer, J. A. Dumont, N. Dodd, K. Nugent, G. Vigliani, A. Luk, A. Brennan, F. Pierce G and A-LONG Investigators, "Phase 3 study of recombinant factor VIII Fc fusion protein in severe hemophilia A," *Blood*, vol. 123, no. 3, pp. 317-325, 2014.

27. M. Recht, L. Nemes, M. Matysiak, M. Manco-Johnson, J. Lusher, M. Smith, P. Mannucci, C. Hay, T. Abshire, A. O'Brien, B. Hayward, C. Udata, D. A. Roth and S. Arkin, "Clinical evaluation of moroctocog alfa, a new generation of B-domain deleted recombinant factor VIII (BDDrFVIII) for treatment of haemophilia A: demonstration of safety, effiacy, and pharmacokinetic equivalence to full-length recombinant factor VIII," *Haemophilia*, vol. 15, no. 4, pp. 869-880, 2009.

28. C. Martinoli, O. D. Alberighi, G. Di Minno, E. Graziano, A. C. Molinari, G. Pasta, G. Russo, E. Santagostino, A. Tagliaferri, A. Tagliafico and M. Morfini, "Development and definition of a simplified scanning procedure and scoring method for Haemophilia Early Arthropathy Detection with Ultrasound (HEAD-US)," *Thrombosis and Haemostasis*, vol. 109, no. 6, pp. 1170-1179, 2013.

29. M. E. A. Schultz, "Evaluating Patient Preference for Haemophilia A Treatment.," *Blood*, vol. 128, no. 22, p. 4973, 2016.

30. FDA, "Code of Federal Regulations.," *Title 21, Volume 1. 21CFR11: Electronic records; electronic signatures*., 01 Apr 2012.

31. EU, "Commission implementing regulation (EU) No 520/2012 of 19 June 2012 on the performance of pharmacovigilance activities provided for in Regulation (EC) No 726/2004 and Directive 2001/83/EC of the European Parliament and of the Council," *Official Journal of the European Union*, 20 Jun 2012.

32. EFPIA, "Code on the Promotion of Prescription-Only Medicines to and Interactions with Healthcare Professionals," Oct 2007.

33. EMA, "ENCePP guide on methodological standards in pharmacoepidemiology.," 05 November 2010.

34. EMA, "GPV Module VI - Management and reporting of adverse reactions to medicinal products (Rev 1)," *Guideline on good pharmacovigilance practices* (EMA/8731138/2011_Rev1), 08 September 2014.

35. EMA, "GPV Module VIII - Post-authorisation safety studies (Rev 1)," *Guideline on good pharmacovigilance practices* (EMA/813938/2011_Rev1), 19 April 2013.

36. EMA, "GPV Module VIII Addendum 1 - Member States' requirements for transmission of information on non-interventional post-authorisation safety studies (Rev 1)," *Guideline on good pharmacovigilance practices* (EMA/395730/2012_Rev 1), 19 April 2013.

37. ICH, "ICH Harmonized Tripartite Guideline: Clinical Safety Data Management: Definitions and Standards for Expedited Reporting (E2D)," Nov 2003.

38. C. Graf, W. P. Battisti, D. Bridges, V. Bruce-Winkler, J. M. Conaty, J. M. Ellison, E. A. Field, J. A. Gurr, M. E. Marx, M. Patel, C. Sanes-Miller and Y. E. Yarker, "International Society for Medical Publication Professionals. Research Methods & Reporting. Good publication practice for communicating company sponsored medical research: the GPP2 guidelines," *BMJ*, 2009.

39. E. von Elm, D. G. Altman, M. Egger, S. J. Pocock, P. C. Gøtzsche and J. P. Vandenbroucke, "STROBE-Initiative. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting of observational studies. J Clin Epidemiol. 2," *J Clin Epidemiol*., 2008.

40. K. Fischer, R. Ljung, H. Platokouki, R. Liesner, S. Claeyssens, E. Smink and H. M. van den Berg, "Prospective observational cohort studies for studying rare diseases: the Europena PedNet Haemophilia Registry," *Haemophilia*, vol. 20, no. 4, pp. 280-6, 2014.

41. V. S. Blanchette, N. S. Key, L. R. Ljung, M. J. Manco-Johnson, H. M. Van den Berg and A. Srivastava, "Definitions in hemophilia: communication from the SSC of the ISTH," *J Thromb Haemost*, vol. 12, no. 11, pp. 1935-1939, 2014.

42. L. P. Solimeno, M. A. Escobar, S. Krassova and S. Seremetis, "Major and Minor Classifications for Surgery in People with Hemophilia: A Literature Review," Clinical and *Applied Thrombosis/Hemostasis*, vol. 24, no. 4, pp. 549-559, 2018.

Annex 1: List of stand-alone documents

Table 6: List of stand-alone documents

Document Name	Final version and date (if available)*
<Physician list>	tbd
<Country & Site list>	tbd
<Steering/Publication Committee Members>	tbd
<Steering/Publication Committee Charter>	v 0.1, 17 OCT 2018 <draft>
<Study timelines and milestone update>	tbd
<CRF>	v 2.0, 04 MAR 2019
<EDC System>	tbd
<EDC System Validation>	tbd
<DMP>	tbd
<SAP>	tbd
<MRP>	tbd
<QRP>	tbd
<Description of data quality improvement measures>	tbd

* Draft versions are indicated by <draft> in brackets and date. “tbd” indicates documents that are not available at the time of protocol creation, but will be issued at a later stage

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

Study title:	HEM-POWR: Observational Study Evaluating Effectiveness and Safety of Real-World Treatment with Damoctocog alfa pegol in Previously Treated Patients with Hemophilia A

EU PAS Register® number:
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[2]	☒	☐	☐	6
1.1.2 End of data collection[3]	☒	☐	☐	6
1.1.3 Progress report(s)	☒	☐	☐	6
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:	☒	☐	☐	7,8,9
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

Comments:

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

[2] 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.

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

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)	☒	☐	☐	9.3.7
5.2	Does the protocol address the validity of the exposure measurement? (e.g. precision, accuracy, use of validation sub-study)	☒	☐	☐	9.3.7
5.3	Is exposure categorised according to time windows?	☐	☐	☒	
5.4	Is intensity of exposure addressed? (e.g. dose, duration)	☐	☐	☒	

Section 5: Exposure definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
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 sponsor. Study is without comparator. Study is without comparator.

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)	☒	☐	☐	9.3.7
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)	☒	☐	☐	9.3.9

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)	☒	☐	☐	9.7.1
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**

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)	☐	☒	☐	9.8

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?	☒	☐	☐	9.5
10.3 Are descriptive analyses included?	☒	☐	☐	9.7
10.4 Are stratified analyses included?	☒	☐	☐	9.7

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Section Number**
10.5 Does the plan describe methods for analytic control of confounding?	☒	☐	☐	9.7
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?	☐	☐	☒	

Comments:

Outcome depends on quality of patient diary. No comparisons will be made.

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)	☒	☐	☐	9.6
11.2 Are methods of quality assurance described?	☒	☐	☐	9.8
11.3 Is there a system in place for independent review of study results?	☒	☐	☐	9.8

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?	☒	☐	☐	9.7
12.1.2 Information bias?	☒	☐	☐	9.7
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).	☒	☐	☐	9.7
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)	☒	☐	☐	9.5

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

Section 13: Ethical/data protection issues	**Yes**	**No**	**N/A**	**Section Number**
13.2 Has any outcome of an ethical review procedure been addressed?	☐	☒	☐	
13.3 Have data protection requirements been described?	☒	☐	☐	10.6

Comments:

No relevant outcomes of an ethical review procedure are necessary for inclusion.

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:

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 author of the protocol: PPD

Date: dd/M PPD , 25/03/2019

Signature:

Note: ENCeP otocols (Revision 4, adopted by ENCePP on 15/10/2018)

Annex 3: Reasons for prophylaxis dosing decision

Select top 3 reasons:

- Age.
- Intravenous access.
- Current treatment regimen.
- Bleeding history with current treatment regimen.
- Prior history of life-threatening bleeding.
- Number of affected joints.
- PK data.
- Adherence/compliance history.
- Activity level.
- Patient/caregiver preference.
- Caregiver support.
- Insurance coverage (US).
- Institution guidelines.
- Country guidelines.
- Other:_____.

Rank in order of importance with 1 being the most important and 3 being the least important.

Annex 4: Definitions: bleeding severity, response to treatment, and surgery

Bleeding severity [40]

- **Minor:** Bleed characterized by mild pain, minimal swelling, minimal restriction of motion/function, resolving within 24 hours of initial treatment.
- **Major:** Bleed characterized by pain, swelling, limitation of motion/function and failure to respond within 24 hours of treatment.

Response to treatment [41]

- **Excellent:** abrupt pain relief and /or improvement in signs of bleeding within approximately 8 hours after a single infusion.
- **Good:** definite pain relief and/or improvement in signs of bleeding within approximately 8 hours after an infusion, but possibly requiring more than 1 infusion for complete resolution.
- **Moderate:** slight beneficial effect within approximately 8 hours after the first infusion, usually requiring more than 1 infusion.
- **No response:** no improvement or condition worsens within approximately 8 hours.

Major and minor surgery [42]

- **Major surgery:** is defined as any surgical or invasive procedure (elective or emergent) in which the overall bleeding risk may have been excessive, would have required a general anaesthesia in an individual without a bleeding disorder, penetrated or exposed a major body cavity, could have resulted in substantial impairment of physical or physiological functions, or required special anatomic knowledge or manipulative skill (e.g., tonsillectomy, laparotomy, thoracotomy and joint replacement)
- **Minor surgery:** is defined as any surgical procedure that did not meet the definition of major, and may have included simple dental extractions, incision and drainage of abscesses, or simple excisions. More than half these surgeries were dental extractions or other dental procedures.

Annex 5: Specific adverse drug reaction follow-up questionnaires

Questionnaire_Hypersensitivity.pdf

Questionnaire_LODE and Inhibitor.pdf

Questionnaire_Neurocognitive disorders.pd

Questionnaire_Renal Impairment.pdf

Annex 6: Description of amendments

AM01: Local amendment for Japan

AM01; 18 MAR 2019	
Protocol section	**Description**
Cover Page	Local Amendment Cover Page (including signature field for Country Medical Director, Pharmacovigilance Country Head, and Head of Post-marketing Surveillance) was added
3.1 Study initiator and funder	J-PMS Conduct Responsible and J-PMS TA Head Hematology were added.
2. List of abbreviations 4. Abstract - Research question and objectives - Variables 8.2 Secondary objectives 9.1.2 Secondary endpoints Table 3 9.3.2 Variables to determine the primary endpoint 9.3.10 Patient-reported outcomes 9.4 Data sources 9.7.4 Analysis of effectiveness variable 9.7.6 Analysis of patient-reported outcomes	Japanese-specific amendment was made: The statement of patient-reported outcomes (Hemo-SAT A, Hemo-QoL [A and SF] and WPAI [+ CIQ: HS]) was deleted. Japanese-specific statement was added in 9.3.10: Patient reported outcomes specified in this protocol will not be applicable for Japanese population.
7.2 Rationale	Japanese-specific statement was added: The sub-study of HEM-POWR will not be applicable for Japanese population.
9.1 Study design	Additional information relating to the number of patients, observation period, interim/final analyses, and the re-examination package for Japanese population included**:** For Japanese population, 60 patients will be observed as safety analysis set. Observation period of Japanese population will be 24 months as defined in Japan risk-management plan. The interim analysis will be conducted when 60 patients are enrolled (i.e. baseline), and the re-examination package will be prepared using

	the data of 24-month observation period.
9.2.2.1 Inclusion criteria	Japanese-specific criteria were added: For Japanese population, hemophilia A patients are treated with damoctocog alfa pegol according to the product label in Japan.
9.2.7 Visits	Japanese-specific statement was added: For Japanese population, patients will be observed at least for the period defined in Japan risk-management plan as regulatory requirement.
Table 3	Japanese -specific amendment was made: The statement of patient infusion diary was deleted.
9.3.2 Variables to determine the secondary endpoints	Japanese-specific statement was added: Joint health measured by HJHS if available (Japan).
9.3.4 Hemophilia Disease history	Japanese-specific statement was added: Ultrasound scanning (Hemophilia Early Arthropathy Detection with Ultrasound [HEAD-US]) to evaluate joints of patients with hemophilic arthropathy [28]. if available (Japan)
9.3.7 Exposure/treatment	Japanese-specific statement was added: For Japanese population, the assay information will be collected if PK is measured.
9.3.12 Anti-PEG antibody measurement	Because of regulatory requirement in Japan, Japanese-specific section was added: 9.3.12 Anti-PEG antibody measurement For Japanese population, data documented by the physician, if collected, include: • Date of blood collection for antibody measurement. • Antibody (no/yes) • Titer of Anti-PEG antibody • Relevant AE (if any)
9.6 Data management	Japanese-specific statement was added: As for patient-report data on bleeds and infusions in Japanese population, physicians will refer to a patient diary which is used routinely in each site.
10.2 Regulatory authority approvals/authorizations	Clarification of conduct of study in accordance with Japanese regulations included: For the Japanese population, this study is conducted in accordance with Article 14-4 (re-examination) of the Pharmaceutical Affairs Law, and Good Post-marketing Surveillance Practice (GPSP) from

	a ministerial ordinance of Ministry of Health, Labor and Welfare (MHLW).
11.4 Evaluation	Japanese-specific statement was added: The safety focus of Japanese population will be considered according to the Japan risk-management plan.
12 Plans for disseminating and communicating study results	Clarification of conduct of study in accordance with Japanese regulations included: For Japanese population, study reports (e.g. periodical safety update report, re-examination package) will be provided to PMDA as defined in the Japanese regulation.
Annex 7	Global signatories removed. Signature pages for J-PMS Conduct Responsible and J-PMS TA Head Hematology were added.

Annex 7: Signature pages

Signature Page - OS Conduct Responsible

Title	HEM-POWR: Observational Study Evaluating Effectiveness and Safety of Real-World Treatment with Damoctocog alfa pegol in Previously Treated Patients with Hemophilia A
Protocol version and date	v1.1, 18 MAR 2019
IMPACT study number	20002
Study type/Study phase	Observational, Phase IV ☐ non-PASS ☒ PASS Joint PASS: ☐ YES ☒ NO
EU PAS register number	Study not yet registered
Medicinal product	Damoctocog alfa pegol
Study Initiator and Funder	Bayer Consumer Care AG, Basel, Switzerland

The undersigned confirms that s/he agrees that the study will be conducted under the conditions described in the protocol.

Print Name: PPD

Date, Signature: 21 March 2019, PPD

Signature Page - Qualified Person responsible for Pharmacovigilance (QPPV)

Title	HEM-POWR: Observational Study Evaluating Effectiveness and Safety of Real-World Treatment with Damoctocog alfa pegol in Previously Treated Patients with Hemophilia A
Protocol version and date	v1.1, 18 MAR 2019
IMPACT study number	20002
Study type/Study phase	Observational, Post-approval ☐ non-PASS ☒ PASS Joint PASS: ☐ YES ☒ NO
EU PAS register number	Study not yet registered
Medicinal product	Damoctocog alfa pegol
Study Initiator and Funder	Bayer Consumer Care AG, Basel, Switzerland

The undersigned confirms that s/he agrees that the study will be conducted under the conditions described in the protocol.

Print Name: PPD

Date, Signature: 21/3/2019, PPD

Signature Page - MAH contact person (Regulatory Affairs)

Title	HEM-POWR: Observational Study Evaluating Effectiveness and Safety of Real-World Treatment with Damoctocog alfa pegol in Previously Treated Patients with Hemophilia A
Protocol version and date	v1.1, 18 MAR 2019
IMPACT study number	20002
Study type/Study phase	Observational, Post-approval ☐ non-PASS ☒ PASS Joint PASS: ☐ YES ☒ NO
EU PAS register number	Study not yet registered
Medicinal product	Damoctocog alfa pegol
Study Initiator and Funder	Bayer Consumer Care AG, Basel, Switzerland

The undersigned confirms that s/he agrees that the study will be conducted under the conditions described in the protocol.

Print Name: PPD

Date, Signature:_____, _____

Note: Refer to the page 72 as Signature Page - Regulatory Affairs responsible.

Signature Page - OS Safety Lead

Title	HEM-POWR: Observational Study Evaluating Effectiveness and Safety of Real-World Treatment with Damoctocog alfa pegol in Previously Treated Patients with Hemophilia A
Protocol version and date	v1.1, 18 MAR 2019
IMPACT study number	20002
Study type/Study phase	Observational, Post-approval ☐ non-PASS ☒ PASS Joint PASS: ☐ YES ☒ NO
EU PAS register number	Study not yet registered
Medicinal product	Damoctocog alfa pegol
Study Initiator and Funder	Bayer Consumer Care AG, Basel, Switzerland

The undersigned confirms that s/he agrees that the study will be conducted under the conditions described in the protocol.

Print Name: PPD

Date, Signature: March 26, 2019 PPD

Signature Page - OS Medical Expert

Title	HEM-POWR: Observational Study Evaluating Effectiveness and Safety of Real-World Treatment with Damoctocog alfa pegol in Previously Treated Patients with Hemophilia A
Protocol version and date	v1.1, 18 MAR 2019
IMPACT study number	20002
Study type/Study phase	Observational, Post-approval ☐ non-PASS ☒ PASS Joint PASS: ☐ YES ☒ NO
EU PAS register number	Study not yet registered
Medicinal product	Damoctocog alfa pegol
Study Initiator and Funder	Bayer Consumer Care AG, Basel, Switzerland

The undersigned confirms that s/he agrees that the study will be conducted under the conditions described in the protocol.

Print Name: PPD

Date, Signature: 21/3/2019, PPD

Signature Page - OS Statistician

Title	HEM-POWR: Observational Study Evaluating Effectiveness and Safety of Real-World Treatment with Damoctocog alfa pegol in Previously Treated Patients with Hemophilia A
Protocol version and date	v1.1, 18 MAR 2019
IMPACT study number	20002
Study type/Study phase	Observational, Post-approval ☐ non-PASS ☒ PASS Joint PASS: ☐ YES ☒ NO
EU PAS register number	Study not yet registered
Medicinal product	Damoctocog alfa pegol
Study Initiator and Funder	Bayer Consumer Care AG, Basel, Switzerland

The undersigned confirms that s/he agrees that the study will be conducted under the conditions described in the protocol.

Print Name: PPD PPD

Date, Signature: 22-MAR-2019, _____

Signature Page - OS Data Manager

Title	HEM-POWR: Observational Study Evaluating Effectiveness and Safety of Real-World Treatment with Damoctocog alfa pegol in Previously Treated Patients with Hemophilia A
Protocol version and date	v1.1, 18 MAR 2019
IMPACT study number	20002
Study type/Study phase	Observational, Post-approval ☐ non-PASS ☒ PASS Joint PASS: ☐ YES ☒ NO
EU PAS register number	Study not yet registered
Medicinal product	Damoctocog alfa pegol
Study Initiator and Funder	Bayer Consumer Care AG, Basel, Switzerland

The undersigned confirms that s/he agrees that the study will be conducted under the conditions described in the protocol.

Print Name: PPD

Date, Signature: 21 Mar 2019, PPD

Signature Page - OS Epidemiologist

Title	HEM-POWR: Observational Study Evaluating Effectiveness and Safety of Real-World Treatment with Damoctocog alfa pegol in Previously Treated Patients with Hemophilia A
Protocol version and date	v1.1, 18 MAR 2019
IMPACT study number	20002
Study type/Study phase	Observational, Post-approval ☐ non-PASS ☒ PASS Joint PASS: ☐ YES ☒ NO
EU PAS register number	Study not yet registered
Medicinal product	Damoctocog alfa pegol
Study Initiator and Funder	Bayer Consumer Care AG, Basel, Switzerland

The undersigned confirms that s/he agrees that the study will be conducted under the conditions described in the protocol.

Print Name: PPD

Date, Signature: 25.3.19, PPD

Signature Page - OS Health Economics and Outcomes Research responsible

Title	HEM-POWR: Observational Study Evaluating Effectiveness and Safety of Real-World Treatment with Damoctocog alfa pegol in Previously Treated Patients with Hemophilia A
Protocol version and date	v1.1, 18 MAR 2019
IMPACT study number	20002
Study type/Study phase	Observational, Post-approval ☐ non-PASS ☒ PASS Joint PASS: ☐ YES ☒ NO
EU PAS register number	Study not yet registered
Medicinal product	Damoctocog alfa pegol
Study Initiator and Funder	Bayer Consumer Care AG, Basel, Switzerland

The undersigned confirms that s/he agrees that the study will be conducted under the conditions described in the protocol.

Print Name: PPD PPD

Date, Signature: 22.03.2019 _____

Signature Page - Regulatory Affairs responsible

Title	HEM-POWR: Observational Study Evaluating Effectiveness and Safety of Real-World Treatment with Damoctocog alfa pegol in Previously Treated Patients with Hemophilia A
Protocol version and date	v1.1, 18 MAR 2019
IMPACT study number	20002
Study type/Study phase	Observational, Post-approval ☐ non-PASS ☒ PASS Joint PASS: ☐ YES ☒ NO
EU PAS register number	Study not yet registered
Medicinal product	Damoctocog alfa pegol
Study Initiator and Funder	Bayer Consumer Care AG, Basel, Switzerland

The undersigned confirms that s/he agrees that the study will be conducted under the conditions described in the protocol.

Print Name: PPD PPD

Date, Signature: 22-03-2019, PPD

Signature Page - OS Real World Evidence Strategy Lead

Title	HEM-POWR: Observational Study Evaluating Effectiveness and Safety of Real-World Treatment with Damoctocog alfa pegol in Previously Treated Patients with Hemophilia A
Protocol version and date	v1.1, 18 MAR 2019
IMPACT study number	20002
Study type/Study phase	Observational, Post-approval ☐ non-PASS ☒ PASS Joint PASS: ☐ YES ☒ NO
EU PAS register number	Study not yet registered
Medicinal product	Damoctocog alfa pegol
Study Initiator and Funder	Bayer Consumer Care AG, Basel, Switzerland

The undersigned confirms that s/he agrees that the study will be conducted under the conditions described in the protocol.

PPD

18/3/19

PPD