Document Type:	Study protocol
Official Title:	Post-marketing investigation (PMI) to assess safety and efficacy of Jivi (BAY 94-9027) treatment in patients with hemophilia A
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Title Page

Protocol Title:

Post-marketing investigation (PMI) to assess safety and efficacy of Jivi (BAY 94-9027) treatment in patients with hemophilia A

Protocol Number: 19764

Amendment Number: 1

Compound Number: BAY 94-9027 / Damoctocog alfa pegol; Human Pegylated rFVIII; Jivi®

Study Phase: Phase IV

Short Title: Jivi interventional PMI study to assess safety and efficacy

Sponsor Name: Bayer Consumer Care AG

Legal Registered Address:

Bayer Consumer Care AG, Peter-Merian-Strasse 84, 4052 Basel, Switzerland

Regulatory Agency Identifier Number(s):

EudraCT: 2018-003655-37

Approval Date: 04 FEB 2020

Sponsor Signatory

PPD

PPD

PPD

PPD

Date

Medical Monitor (Study Medical Expert) name and contact information can be found in the Trial Master File (TMF).

Protocol Amendment Summary of Changes Table

DOCUMENT HISTORY	
Document	***Date***
Amendment 1	04 FEB 2020
Original Protocol	19 MAR 2019

Amendment 1 (04 FEB 2020)

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union, as it includes a new criterion for premature termination of the study. Nevertheless, it neither significantly impacts the safety or physical/mental integrity of participants nor the scientific value of the study.

Overall Rationale for the Amendment:

This amendment was prepared to incorporate Health Authority feedback regarding the definitions for both the end of study and adverse events, assess body weight at additional visits, and to clarify the number of times a participant may be rescreened.

Section # and Name	Description of Change	Brief Rationale
1.3 Schedule of Activities 8.2.2 Physical Examinations 10.4.4 Visit 4 – ED 50-75 (Month 6 ± 14 days) 10.4.6 Visit 6 if needed – ED 50-75 (Month 18 ± 14 days)	Body weight measurement has been added to Visits 4 and 6.	Body weight will be assessed every 6 months in order to avoid underdosing.
4.4 End of study definition	Definition for the end of the overall study changed The end of the overall study is defined as LPLV and the last data from the last visit are received. For each participating country, end of study is achieved with LPLV in that country.	Align end of study with planned trial activities for participants.
4.4 End of Study Definition	Criteria added for premature termination of the study.	Define stop criteria for premature termination of the study.
5.4 Screen Failures	Section updated to specify that screen failures may be rescreened once.	Define maximum number of times a participant may be rescreened.
6.2 Preparation/ Handling/Storage/Accountability	Instructions updated to more accurately describe the instructions for management of study intervention.	Reflects current sponsor standard.
10.1.1 Regulatory and Ethical Considerations	References to region-specific laws removed	Remove redundancy, as these laws are covered by "...all other applicable local regulations."

Section # and Name	Description of Change	Brief Rationale
10.2 Appendix 2: Clinical Laboratory Tests	Addition of albumin/creatinin ratio, Beta-2microglobulin.	Clarification that the biomarker albumin will be assessed through the albumin/creatinine ratio. Beta-2microglobulin was erroneously identified as alpha-2microglobulin.
10.3.1 Definition of AE	Requirements for laboratory test results modified	Agency request
10.3.4 Reporting of SAEs	Reporting instructions updated to refer to email instead of facsimile transmission.	Reflects current sponsor standard.

Typographical, grammatical, and other minor edits are not identified.

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1. Protocol Summary

1.1 Synopsis

Protocol Title: Post-marketing investigation (PMI) to assess safety and efficacy of Jivi (BAY 94-9027) treatment in participants with hemophilia A

Short Title: Jivi interventional study to assess safety and efficacy

Rationale: This study aims to collect clinical data in at least 25 participants, to comply with the post-marketing requirements to collect safety data of 200 participants treated with at least 100 exposure days (ED) including participants from pre-authorization studies, according to EMA FVIII guideline requirements EMA/CHMP/BPWP/144533/2009 rev.2 (EMA 2017).

Objectives and Endpoints:

Objectives	Endpoints throughout the study
Primary	
• To assess safety of Jivi	Primary Endpoint • FVIII inhibitor development by the Nijmegen Bethesda assay. Secondary Endpoints • Treatment-emergent adverse events (TEAE) • Development of treatment-emergent anti-PEG antibodies
Secondary	
• To assess clinical efficacy of Jivi	Secondary Endpoint • Annualized bleeding rate (ABR)

Overall Design:

The study will be a multicenter, single group, uncontrolled open-label trial. Severe hemophilia A patients, age ≥18 years, will be enrolled and treated with prophylaxis treatment and for breakthrough bleeds for at least 100 exposure days (ED), which may require 1-2 years depending on the prophylaxis regimen. Assessment of immunogenicity/safety will be performed at pre-defined ED as required by the EMA FVIII Guideline. The recommended starting dose is every 5 days treatment (45 IU/kg). Response to treatment will be assessed at the next visit after 10-15 ED, scheduled for inhibitor assessment as per Guideline. Participants may be assigned to different dosing regimens (every 7 days or 2x/week) or continue with every 5 days regimen, according to individual bleeding tendency and needs at investigator's discretion. Clinical general safety, efficacy, and immunogenicity will be assessed at baseline, 10-15 ED, 50-75 ED and after approximately 100 ED.

This study will address regulatory requirements of assessment of safety in a total of 200 participants with 100 ED including pre-licensure participants of the development program from the studies #13024 Protect VIII and #15912 Protect Kids. This study will include at least 25 participants for fulfillment of the requirement and provide a pooled analysis of all clinical studies (phase III/IV) including at least 200 participants observed for at least 100 ED.

The study will assess the important identified risks of development of Factor VIII (FVIII) inhibitors, hypersensitivity, and potential lack of drug effect associated with anti-polyethylene glycol (PEG) antibodies during the first exposures to Jivi and long-term treatment up to 100

ED. An optional interim analysis will be performed, if needed for regulatory submission or publication purposes, after all participants have been treated for 6 months.

Intervention Model: Single Group

Primary Purpose: Treatment

Number of Arms: Single arm

Masking: No masking

Number of Participants: Approximately 25-30 participants will be assigned to the study intervention. At least 25 participants are expected to complete the study. The study is completed when 25 participants have reached 100 ED.

Intervention Groups and Duration:

All participants will be treated with three possible prophylactic regimens: 2x/week, every 5 days, or every 7 days with a recommended starting regimen of every 5 days. Participants are allowed to change the dose frequency during the study. All treatment decisions for identifying appropriate prophylactic treatment regimens should be guided by clinical judgement based on individual participant characteristics and treatment response.

The total treatment duration is the time to reach 100 exposure days (ED) of Jivi. The total duration of study participation for each participant may require up to 2 years depending on the selected prophylactic regimen. After the end of the study, the participants will be offered the option to participate in a non-interventional PASS study. While the decision for dose adjustment is at the investigator's discretion based on patient clinical characteristics, the following recommendations are provided: the starting dose is 45 IU/kg every 5 days. Investigator may assess if dose regimen adjustment is warranted at the next planned visit (10-15 ED). A participant with zero bleed during the first 8-10 weeks of treatment may be considered for every 7 days at 60 IU/kg; a participant with 1 clinically relevant bleed during the first 8-10 weeks may be considered to either continue treatment every 5 days while at the 60 IU/kg or switch to twice weekly at 40 IU/kg; and a participant with ≥ 2 clinically relevant bleeds during the first 8-10 weeks should be changed to twice weekly at 40 IU/kg.

The details about duration and recommended dose regimen of study participation are as follows:

Recommended dose regimen

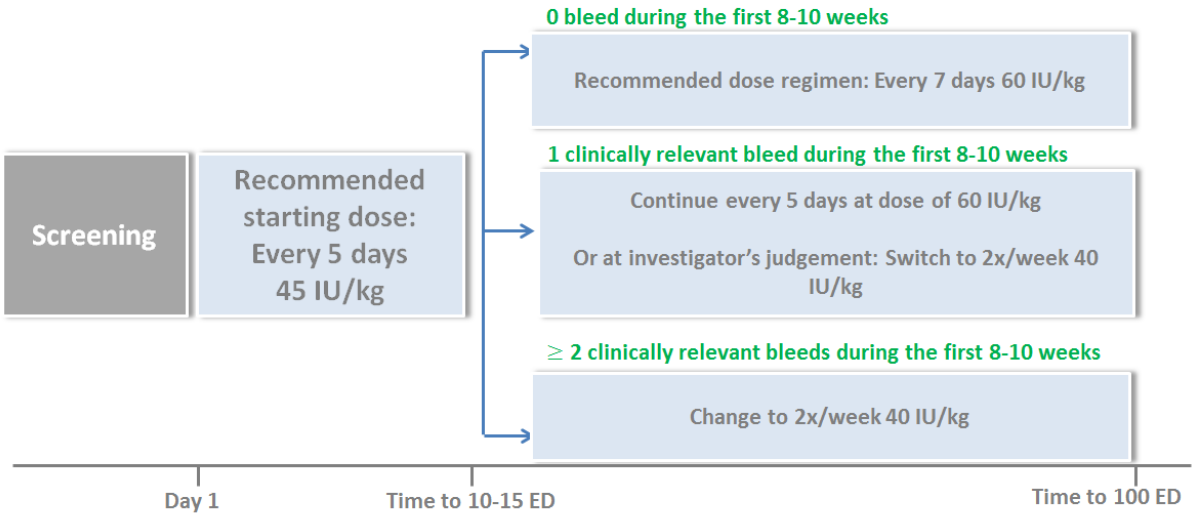
Procedure	Duration	Dose regimen		Route of administration
Screening	> 2 weeks, ≤ 8 weeks	Continuation of previous treatment		
Treatment Phase	Time to reach 10-15 ED (8 to 10 weeks)	Recommended starting dose 45 IU/kg every 5 days. Dose regimen can be adjusted any time in case of bleeds		IV injection
	Time to reach 100 ED	0 bleed during the first 8-10 weeks:	Recommended dose regimen: 60 IU/kg every 7 days	IV injection
		1 clinically relevant bleed during the first 8-10 weeks:	Continue every 5 days at dose of 60 IU/kg Or at investigator's judgement: Switch to 40 IU/kg 2x/week	
		≥ 2 clinically relevant bleeds during the first 8-10 weeks:	Change to 40 IU/kg 2x/week	

ED = exposure day, IV = intravenous
Clinically relevant: joint or muscle bleed that need treatment

Data Monitoring Committee: No

1.2 Schema

Figure 1–1 Schema for suggested dose changes in response to bleeding



ED = exposure day
Clinically relevant: joint or muscle bleed that need treatment
Note: Participants are allowed to change the dose regimen during the study. All treatment decisions for identifying appropriate prophylactic treatment regimens should be guided by clinical judgement based on individual patient characteristics and treatment response

1.3 Schedule of Activities (SoA)

Table 1–1 Study Schedule of Activities (SoA)

Procedures	Screening [a]	Baseline Pre-dose	ED 10-15	ED 50-75 Every 6 months			End of study 100 ED / Early Termination
	Visit 1 2-8 Wks before baseline	Visit 2 Day 1	Visit 3 Wk 8-10 [b]	Visit 4 Month 6 (±14 days) [c]	Visit 5 Month 12 (±14 days) [c]	Visit 6 Month 18 if needed (±14 days) [c]	Last Visit (+14 days)
Informed consent (inclusion)	X						
HIV screening [d]	X						
Inclusion and exclusion criteria	X	X					
Demography(including gene defect)	X						
Full physical examination including neurological standard assessment, height, and weight	X						X
Body Weight Measurement				X	X	X	
Activity level (type of sports, hrs/wk)	X						
Medical and surgical history (general, disease, family history of hemophilia, and history of inhibitor)	X						
Activity tracker	X	X		X	X		X [e]
Previous medication (medication history)	X						
Dose regimen adjustment			X				
Vital signs [f]	X	X					X
Urine sample (routine urinalysis and renal biomarkers)	X	X			X		X
Laboratory assessments (Hematology and clinical chemistry,)	X				X		X
PEG level in plasma	X						X
Immunogenicity (Factor VIII inhibitor, ADA) [g]	X	X	X	X	X		X

Table 1–1 Study Schedule of Activities (SoA)

Procedures	Screening [a]	Baseline Pre-dose	ED 10-15	ED 50-75 Every 6 months			End of study 100 ED / Early Termination
	Visit 1 2-8 Wks before baseline	Visit 2 Day 1	Visit 3 Wk 8-10 [b]	Visit 4 Month 6 (±14 days) [c]	Visit 5 Month 12 (±14 days) [c]	Visit 6 Month 18 if needed (±14 days) [c]	Last Visit (+14 days)
Recovery (pre and 15-30 min post injection FVIII levels) [h]		X	X				X
FVIII level after 48 or 72 hours after last injection				X	X		
In-hospital injection of Jivi		X	X				X
AE review	X	X	X	X	X	X	X
Return used and unused study intervention			X	X	X	X	X
Dispense study intervention for home injections		←==continuously in accordance with IxRS drug dispensing schedule==→					
Injection of Jivi		←====continuously in accordance with assigned treatment regimen===→					
Concomitant medication review	X	←==========continuously==========→					
Patient diary (EPD) documentation	X	←==========continuously==========→					
Interaction between participants and investigators		←==========Monthly contact==========→					

Abbreviations: ADA=anti-drug antibody, AE=adverse event, ALT=alanine aminotransferase, AST=aspartate aminotransferase, ED=exposure days, EPD=electronic patient diary, HIV=human immunodeficiency virus, hrs=hours, IxRS=Interactive voice/web response system, max=maximum, and Wk=week.

a. The time interval between Screening and Baseline visit is 2 to 8 weeks.
b. Although the allowable visit window is ±14 days, visits must occur within the specified ED range.
c. Visits should be scheduled within the visit window so that at least one visit occurs in the 50 – 75 ED range.
d. HIV screening will be performed only in case that negative result in patient documentation is older than 1 year at date of screening.
e. Only in case of Early Termination Visit before V6.
f. In case of any injection related AE, vital signs will be collected in addition post-injection for participants.
g. At Baseline, Visit 3 and End of Study/Early Termination Visit, blood samples for immunogenicity will be collected before the in-hospital injection of Jivi.
h. Recovery should be measured at least 72 h after last injection of FVIII of Jivi.

2. Introduction

Recombinant coagulation FVIII (rFVIII) is a replacement therapy in patients with Hemophilia A.

Jivi (BAY 94-9027) is a recombinant B-domain deleted (BDD) human coagulation FVIII variant expressed in a baby hamster kidney cell line and site specifically conjugated with a 60 kDa, branched (30 kDA each) polyethylene glycol (PEG). Jivi was developed as an extended half-life recombinant FVIII (rFVIII) through PEGylation resulting in a reduced clearance from plasma while retaining the normal activity of the FVIII molecule.

Jivi has received marketing authorization from Food and Drug Administration (FDA), European Medicines Agency (EMA), Japanese Pharmaceuticals and Medical Devices Agency (PMDA), and Health Canada. The approved indication is: Treatment and prophylaxis of bleeding (including perioperative management) in previously treated patients (PTPs) ≥ 12 years of age with hemophilia A (congenital FVIII deficiency).

2.1 Study Rationale

Hemophilia A is caused by deficiency or reduced activity of Factor VIII, a critical component of blood coagulation.

Hemophilia A patients are treated by intravenous administration of FVIII on-demand or as a prophylactic therapy administered two to four times a week with unmodified FVIII products. The need for frequent intravenous injection creates barriers to patient compliance and makes adherence to prophylaxis difficult. Treatment with FVIII products with extended half-life (EHL) are expected to result in significant benefit in long-term outcomes and quality of life improvement for patients with hemophilia. Products with an extended t1/2 have been approved recently in several countries worldwide (such as Elocta®, Eloctate®, Adynovate®) which provide treatment options with dosing intervals of 3 to 5 days for prophylaxis treatment.

Jivi was developed as an EHL- FVIII for prophylaxis, peri-operative management, and treatment of acute bleeding events. Site directed PEGylation was used to increase the FVIII half-life, resulting in a longer duration of the effect by raising plasma levels for a longer duration, thereby allowing for less frequent dosing when used in a prophylaxis setting. Efficacy and safety of Jivi were demonstrated in the pivotal trials (Coyle et al. 2014, Reding et al. 2017).

This study aims to collect clinical data in at least 25 participants, to comply with the post-marketing requirements to collect safety data of 200 participants treated with at least 100 ED including participants from pre-authorization studies, according to the EMA FVIII guideline requirements EMA/CHMP/BPWP/144533/2009 rev.2 (EMA 2017).

2.2 Background

Individuals with severe hemophilia A (<1% functional FVIII) experience frequent and recurrent bleeding into the soft tissue and joints, resulting in joint damage and destruction, as well as significant negative effects on their Quality of life (QoL), psychosocial well-being, education, and financial condition. Factor replacement therapy is used to treat bleeding events

when they occur. However, such "on-demand" therapy is insufficient for the prevention of arthropathy (Aledort et al. 1994, Petrini et al. 1991). International treatment guidelines recommend that all individuals with severe hemophilia should be treated with some form of prophylactic therapy. The efficacy of standard regimens in preventing bleeding events has been confirmed by multiple observational studies (Aledort et al. 1994, Ljung 1998, Lofqvist et al. 1997, Nilsson et al. 1992), and the value of regular infusion starting in early childhood in preventing joint damage was recently confirmed objectively (Manco-Johnson et al. 2007).

Despite recommendations by the World Health Organization (WHO) and World Federation of Hemophilia that prophylaxis should be the standard of care; such treatment has not been uniformly accepted by patients for different reasons. One of the reasons is that the prophylaxis is a time consuming and demanding regimen. In addition, adherence to a regularly scheduled regimen that requires intravenous infusion as often as 3x/week is difficult to maintain.

Jivi was developed as an extended half-life rFVIII through PEGylation resulting in a reduced clearance from plasma while retaining the normal activity of the FVIII molecule. Pharmacokinetics (PK) studies with Jivi demonstrated a prolonged half-life and improved area under the curve (AUC) as compared to unmodified FVIII(Coyle et al. 2014). Clinical efficacy and safety for treatment of bleeds and prophylaxis with 2x/week, every 5 days, and every 7 days have been evaluated in the clinical development program including 232 patients in the age of 2-65 years. Jivi has received market authorization approval for treatment and prophylaxis of bleeding in previously treated patients ≥ 12 years of age with hemophilia A (congenital factor VIII deficiency).

Further information on efficacy and safety of Jivi is provided in the Summary of Product Characteristics (SmPC).

2.3 Benefit/Risk Assessment

Jivi has received marketing authorization by the FDA, EMA, PMDA, and Health Canada for the treatment and prevention of bleeds in patients ≥12 years of age.

Jivi has demonstrated the potential for dosing every 5 days or every 7 days in a majority of participants in clinical studies, offering the option of a prophylaxis treatment with less frequent dosing for hemophilia A patients ≥ 12 years of age. For the patients with increased bleeding tendency, 2x/week treatment with Jivi provided an efficacious treatment option.

As is the case for all FVIII replacement treatments, the most serious expected adverse event (AE) is the development of inhibitory antibodies against FVIII. No new or confirmed inhibitors have been observed during the clinical studies.

Hypersensitivity reactions are a known and listed adverse event for FVIII products and have been reported with use of Jivi. A clinical immune response associated with anti-PEG antibodies, manifested as symptoms of acute hypersensitivity and/or loss of drug effect has been observed within the first 4 exposure days primarily in children < 6 years of age (Study #15912 PROTECT Kids). CCI [redacted] in such cases Jivi should be discontinued and patients switched to a previously effective factor VIII product.

Based on available data and considering the medical need, the benefit risk assessment was considered to be positive by Regulatory Authorities.

More detailed information about the known risks and reasonably expected adverse events of Jivi may be found in the SmPC/ Package Leaflet.

3. Objectives and Endpoints

The objective of the study is to confirm general safety and clinical efficacy with specific focus on immunogenicity and inhibitor documentation in a routine clinical use of the product in at least additional 25 participants during 100 ED in order to fully comply with Guideline requirements of 200 participants observed for at least 100 ED including participants from pre-authorization studies.

Objectives	Endpoints throughout the study
Primary	
• To assess safety of Jivi	Primary Endpoint • FVIII inhibitor development by the Nijmegen Bethesda assay. Secondary Endpoints • Treatment-emergent adverse events (TEAE) • Development of treatment-emergent anti-PEG antibodies
Secondary	
• To assess clinical efficacy of Jivi	Secondary Endpoint • Annualized bleeding rate (ABR) Other pre-specified • Other pre-specified endpoints are specified in statistical analysis plan (SAP)
Other pre-specified	
• CCI [redacted]	• CCI [redacted]

4. Study Design

4.1 Overall Design

The study will be a multicenter, single group, uncontrolled open label trial. Severe hemophilia A patients, age ≥18 years, will be enrolled and treated with prophylaxis treatment and for breakthrough bleeds for at least 100 ED, which may require 1-2 years depending on the

prophylaxis regimen. Assessment of immunogenicity/safety will be performed at pre-defined ED as required by EMA FVIII Guideline.

The recommended starting dose is every 5 days treatment (45 IU/kg)- An assessment of response to treatment will be performed at the next scheduled visit after 10-15 ED (8-10 weeks). Thereafter, participants may be assigned to different dosing regimens (every 7 days or 2x/week) or continue with every 5 days regimen, according to individual bleeding tendency and needs at investigator's discretion. Clinical general safety, efficacy, and immunogenicity will be assessed at baseline, after 10-15 ED, 50-75 ED and after approximately 100 ED.

This study will address regulatory requirements of assessment of safety in a total of 200 participants with 100 ED including pre-licensure participants of the development program from the studies #13024 Protect VIII and #15912 Protect Kids. This study will include at least 25 participants for fulfillment of the requirement and provide a pooled analysis of all clinical studies (phase III/IV) including at least 200 participants observed for at least 100 ED.

The study will assess the important identified risks of development of Factor VIII (FVIII) inhibitors, hypersensitivity, and potential lack of drug effect associated with anti-polyethylene glycol (PEG) antibodies during the first exposures to Jivi and long-term treatment up to 100 ED.

Intervention Groups and Duration:

Participants will be enrolled in the study and start the recommended starting treatment with every 5 days at a dose of 45 IU/kg. Participants with an increase in bleeding frequency may switch to a twice weekly regimen (2x/week, 40 IU/kg) at the investigator's discretion during the first 8-10 weeks.

At the next scheduled visit (after 10-15 ED, 8-10 weeks), all participants will have their bleeding frequencies reviewed by the investigator to determine any adjustment of the treatment. Participants who have no bleeds during the first 8-10 weeks are recommended to have the treatment with every 7 days at a dose of 60 IU/kg. Participants who have 1 clinically relevant bleed (e.g. joint or muscle bleed) during the first 8-10 weeks may continue the treatment with every 5 days at dose of 60 IU/kg; the regimen may also be adjusted to 2x/week (40 IU/kg) at the investigator's discretion after evaluation of bleed risk. If participants have $\geq$ 2 relevant bleeds during the first 8-10 weeks, these participants should change treatment to 40 IU/kg 2x/week. For overweight patients, the maximum total dose per injection should not be higher than approximately 6000 IU (rounded up to full vials).

Participants are allowed to change the dose frequency at any time during the study in case of increase in bleeding frequency. All treatment decisions for identifying appropriate prophylactic treatment regimens should be guided by clinical judgement based on individual participant characteristics and treatment response. It is recommended that the participant increases frequency (if treated every 7 days or every 5 days) after a second spontaneous bleed within a 3-month period.

The total treatment duration is the time to reach 100 (exposure days) ED of Jivi. The total duration of study participation for each participant may require up to 2 years depending on the selected prophylactic regimen. The details about duration and recommended dose regimen of study participation for each study periods are as follows:

Procedure	Duration	Dose regimen		Route of administration
Screening	> 2 weeks, ≤ 8 weeks	Continuation of previous treatment		
Treatment Phase	Time to reach 10-15 ED (8 to 10 weeks)	Recommended starting dose 45 IU/kg every 5 days. Dose regimen can be adjusted any time in case of bleeds		IV injection
	Time to reach 100 ED	0 bleed during the first 8-10 weeks:	Recommended dose regimen: 60 IU/kg every 7 days	IV injection
		1 clinically relevant bleed during the first 8-10 weeks:	Continue every 5 days at dose of 60 IU/kg Or at investigator's judgement: Switch to 40 IU/kg 2x/week	
		≥ 2 clinically relevant bleeds during the first 8-10 weeks:	Change to 40 IU/kg 2x/week	

ED = exposure day, IV = intravenous
Clinically relevant: joint or muscle bleed that need treatment

4.2 Scientific Rationale for Study Design

The study is designed according the requirements defined in the "Guideline on the clinical investigation of recombinant and human plasma-derived factor VIII products" EMA/CHMP/BPWP/144533/2009 rev.2 (EMA 2017). The total sample size was chosen in order to fulfil Guideline requirements of 200 participants observed for at least 100 ED.

4.3 Justification for Dose

The dose is based on the SmPC.

Prophylactic treatment regimens should be guided by clinical judgement based on individual patient characteristics and treatment response.

4.4 End of Study Definition

A participant is considered to have completed the study if he has completed all phases of the study including the last visit or the last scheduled procedure shown in the Schedule of Activities. If more than 25 participants are included, all participants will be treated for at least 6 months, but not all participants may reach 100 ED at the end of the study.

The end of the clinical trial in each participating country is achieved with LPLV in the country. The end of the overall study is defined as LPLV and the last data from the last visit are received.[1]

Primary completion

The primary completion is defined as the date when 25 participants have completed the last visit for the primary outcome.

Premature termination of study

The trial must be stopped if new safety information emerges that can negatively affect the benefit/risk assessment of Jivi or the clinical trial.

5. Study Population

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

At least 25 participants will be included. Medical record to a detailed participant documentation (ie, diary, etc.) covering either the last 150 exposure days or the last 2 years per participant to confirm treatment modality (i.e. prophylaxis, on demand), should be available.

5.1 Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

Age

1. Participants must ≥ 18 years of age inclusive, at the time of signing the informed consent

Type of Participant and Disease Characteristics

2. Participants with severe hemophilia A (FVIII: C<1%)
3. PTPs (≥150 ED) on prophylaxis treatment before enrollment
4. Participants who are immunocompetent. If human immunodeficiency virus (HIV) positive, cluster of differentiation 4 (CD4)+ lymphocyte count >200/mm3
5. Participants who are willing to complete an eDiary

Sex

6. Male participants

[1] Following LPLV, lab result data (e.g. inhibitor results, clinical chemistry, hematology) must be received before the study can be considered completed.

Informed Consent

7. Capable of giving signed informed consent as described in Section 10.1.3 of the protocol which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in the protocol

5.2 Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

Medical Conditions

1. Any other inherited or acquired bleeding disorder in addition to Hemophilia A.
2. Platelet count < 100,000/mm^3
3. Creatinine > 2x upper limit of normal
4. AST or ALT > 5x upper limit of normal (AST: aspartate aminotransferase; ALT: alanine aminotransferase)

Prior/Concomitant Therapy

5. The participant has a planned major surgery.

Prior/Concurrent Clinical Study Experience

6. The participant is currently participating in another investigational drug study, or has participated in a clinical study involving an investigational drug within 30 days of signing informed consent or previous treatment in a clinical phase III study with BAY 94-9027

Diagnostic assessments

7. Current evidence (by central laboratory) or history of inhibitor to FVIII with a titer ≥ 0.6 Bethesda unit (BU).

Other Exclusions

8. Known hypersensitivity to the drug substance, excipients, or mouse or hamster protein.

5.3 Lifestyle Considerations

No restrictions are required.

5.4 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently entered in the treatment phase of the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements

and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse event (SAE).

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened once, and repeat the screening procedures/laboratory tests provided that all screening procedures/laboratory tests are performed within the 8-week screening period. Rescreened participants should be assigned a new participant number.

6. Study Intervention

Study intervention is defined as any investigational intervention(s), marketed product(s), placebo, or medical device(s) intended to be administered to a study participant according to the study protocol.

6.1 Study Intervention(s) Administered

All treatment decisions for identifying appropriate prophylactic treatment regimens should be guided by clinical judgment based on the approved SmPC and the individual participant characteristics and treatment response:

Treatment	Every 5 days	2x/week	Every 7 days
Intervention Name	Jivi		
Type	Biologic		
Dose formulation	Ampule		
Duration of intervention	Up to 100 ED, regimen as per investigator decision		
Unit dose strengths	500, 1000, 2000, or 3000 IU/vial		
Dosage Level(s)	45-60 IU/kg Every 5 days The total recommended maximum dose/injection is approximately 6000 IU (rounded up to vial size).	40 IU/kg Two times per week	60 IU/kg Every 7 days The total recommended maximum dose/injection is approximately 6000 IU (rounded up to vial size).
Route of Administration	IV injection		
IMP and NIMP	IMP (Jivi)		
Sourcing	Provided by the Sponsor		
Packaging and Labeling	Jivi will be provided in glass vials with a prefilled syringe. Each glass vial will be labeled as required per country requirement.		
Current Name / Former Name	Commercial name: Jivi / BAY 94-9027		

ED=exposure day, IMP=Investigational medicinal product, NIMP= Non investigational medicinal product

Treatment of bleeds

All bleeding events that occur in participants receiving prophylactic infusion after the start of treatment (Visit 2) will be treated with Jivi as outlined in the package insert (SmPC). If a bleed occurs on a day of the planned injection, the participant should treat the bleed instead of receiving the scheduled prophylactic infusion.

The infusion schedule with Jivi is not affected by the treatment of bleeds, eg, if a participant treats a bleed on Sunday and is due to infuse his prophylactic dose on Monday, he will still receive the scheduled infusion. If a repeated treatment for the bleed is required, the dose administered on the scheduled infusion day may be modified to ensure the participant receives appropriate treatment.

6.2 Preparation/Handling/Storage/Accountability

Instructions for the preparation of study interventions can be found in the leaflet for using Jivi.

All study interventions will be stored at the investigational site in accordance with Good Clinical Practice (GCP) and Good Manufacturing Practice (GMP) requirements and the instructions given by the clinical supplies department of the sponsor or its affiliates.

Special storage conditions and a complete record of batch numbers and expiry dates can be found in the sponsor's study file; the site-relevant elements of this information will be available in the investigator site file. On the day of receipt, the responsible site personnel will confirm receipt of study intervention via IxRS.

1. The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study intervention received and any discrepancies are reported and resolved before use of the study intervention.
2. Only participants enrolled in the study will receive study intervention and only authorized site staff will supply or administer study intervention. All study intervention must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff.
3. The investigator, or the head of the institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation, and final disposition records).
4. Further guidance and information for the final disposition of unused study interventions are provided in a separate document.

6.3 Measures to Minimize Bias: Randomization and Blinding

This is an open-label study, and no randomization or masking will be performed.

Participants will be identified by a unique participant number with 9 digits once the ICFs are signed. The first 5 digits will identify the country and study site, the last 4 digits are assigned to the participant of the specific site in increasing order.

6.4 Study Intervention Compliance

Participant compliance with study intervention will be assessed at each visit.

Used and unused vials of study medication will be returned to the clinic at every site visit for accounting. Any discrepancies between actual and expected amount of returned vials must be discussed with the participant at the time of the visit, and any explanation must be documented in the source records.

The electronic patient diary (EPD) will be used to assess the participant's compliance with the treatment schedule/dose, and to reconcile study medication inventory. The EPD will be used to record date and time of self-administration of study intervention for prophylaxis as well as every bleeding episode with details of the bleeding and administered intervention. Data on the EPD will be transmitted on a regular basis.

The EPD will be reviewed at visits and at regular contacts with the participant during the study.

6.5 Prior and Concomitant Therapy

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements) that the participant is receiving at the time of enrollment or receives during the study must be recorded along with:

- Reason for use
- Dates of administration including start and end dates
- Dosage information including dose and frequency

The Medical Monitor (Study Medical Expert) should be contacted if there are any questions regarding concomitant or prior therapy.

Bleeds which occur during the screening period (Screening visit until Visit 2) will be treated with the participant's previous FVIII product.

All medications and blood products required by the participant after the informed consent is signed, including FVIII products other than study intervention, will be listed in the appropriate CRF. All concurrent prescription and non-prescription medications including over-the-counter and alternative preparations (including herbal remedies, vitamins, and health food supplements), antibiotics and pain medications being administered starting at least 3

months previous to the study will be recorded in the CRF at screening and throughout the treatment and follow-up periods.

The participant should not be taking any other investigational drug while receiving treatment with Jivi.

Medications which cause a bleeding diathesis (for example, Aspirin® or any acetylsalicylic acid) should be avoided in individuals with hemophilia, except as specifically prescribed by a treating physician. Low dose Aspirin should not be discontinued in participants who have been identified to be at risk for cardiovascular events. The decision to prescribe non-steroidal anti-inflammatory drugs, Cyclooxygenase-2 (COX-2) inhibitors, or brief courses of corticosteroids to treat pain or acute synovitis is at the discretion of the treating physician.

Inhaled or topical steroid medications (as for the treatment of asthma or eczema) are allowed. Brief courses of prednisone/methylprednisolone (< 14 days) for treatment of disorders such as synovitis, asthma, etc. are at the discretion of the treating physician. For any participant requiring longer courses of corticosteroids or use of other immunomodulatory treatment, the investigator should notify the sponsor.

6.6 Dose Modification

This protocol allows some alterations from the currently outlined dosing schedule, but the maximum dose must not exceed approximately 60 IU/kg for every 5 days and every 7 days treatments and approximately 40 IU/kg for 2x/week treatment, and for patients with overweight, the dose per injection should not be higher than approximately 6000 IU, rounded up to full vials. Dose adaptations according to participant needs and at the investigator's discretion are allowed within the approved dose range and rounding up to full vials which may result in slightly higher dosages.

6.7 Intervention after the End of the Study

After completion of the study, treatment with study intervention will end. Subsequent treatment will be mutually agreed upon by the participants and the investigator.

7. Discontinuation of Study Intervention and Participant Discontinuation/Withdrawal

7.1 Discontinuation of Study Intervention

- Inhibitor development

  Any inhibitor development (≥0.6 BU/mL, confirmed) is considered a SAE. Discontinuation of study intervention due to a high titer inhibitor development (titer > 5 NBU/mL) should be considered by the investigator if the investigator believes that it is in the best interest of the participant and/or if bypassing agents are needed to treat bleeds. Participants who discontinue study intervention due to inhibitor development cannot continue in the study and will be withdrawn.

- Planned major surgery during the study

  If the participant has a planned elective surgery during the study, the investigator and sponsor will determine if the participant can continue in the study and if any change in participant management is needed.

See the SoA for data to be collected at the time of intervention discontinuation and for any further evaluations that need to be completed.

7.1.1 Temporary Discontinuation from Study Intervention

Participants who have an elective major surgery during the study may be treated with other FVIII, according to local practice at the discretion of investigators. Participants will resume their treatment assignment of Jivi as per this protocol after surgical recovery.

7.2 Participant Discontinuation/Withdrawal from the Study

A participant who withdraws is one who discontinues from a clinical study for any reason. The participant will not suffer any disadvantage as a result.

- A participant may withdraw from the study at any time at his own request without giving reasons, or may be withdrawn at any time at the discretion of the investigator for safety, behavioral, compliance, or administrative reasons..
- At the time of discontinuing from the study, if possible, an early discontinuation/final visit should be conducted, as shown in the SoA. See SoA for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.
- The participant will be permanently discontinued both from the study intervention and from the study at that time.
- If the participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.
- A participant must be withdrawn from the study if the development of an inhibitory antibody to Jivi that neutralizes activity sufficiently to interfere with effective treatment or requires use of a bypassing agent to treat bleeds.
- A participant must be withdrawn from the study if he fails to comply with scheduled appointments for the study-related evaluations and with EPD data entry to an extent that compromises collection of critical data.
- A participant must be withdrawn from the study if significant concurrent illness or deterioration occurs in the participant’s condition, including laboratory values that the investigator deems to be incompatible with the participant’s continued safe participation in the study.

7.3 Lost to Follow Up

A participant will be considered lost to follow-up if he repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow up, the investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, he will be considered lost to follow up.

8. Study Assessments and Procedures

- Study procedures and their timing are summarized in the SoA and visit description Section 10.4. Protocol waivers or exemptions are not allowed.
- Immediate safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study intervention.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria.
- Procedures conducted as part of the participant's routine clinical management (e.g., blood count) and obtained before signing of the ICF may be utilized for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the SoA.
- If deemed necessary for an individual participant, the investigator or designee, at his/her discretion, may arrange visits in addition to the scheduled study visits. Unscheduled visits will be documented in the eCRF.

8.1 Efficacy Assessments

This is a post authorization safety study (PASS). The efficacy endpoints are secondary endpoints for the study and include:

Secondary Endpoints throughout the study

- ABR

Other exploratory endpoints pre-specified throughout the study

- Percentage of participant with 0 spontaneous bleeds during a 6-month treatment
- Total number of exposures
- Consumption: dose/kg per participant/year
- Type, location and severity of bleeds, reason for each injection, and response to treatment of bleeds

Further endpoints are specified in the SAP.

8.1.1 Treatment Logs/Bleeding Verification

Treatment logs are commonly used for hemophilia participants for documentation of their home treatment. Home treatment and bleeding information are the key variables for evaluation of efficacy. Study specific treatment logs will be provided in national language. The system for this study will be electronic patient diary (EPD) devices since they are interactive, allow for real time data transmission, record-stamp date and time of fulfillment and facilitate the clarification of data with the site and also the data cleaning process. Participants will be provided with EPDs for the whole study. At Screening visit, participants will be trained in the use of the device. These logs will be used to collect the treatment data and bleeding episodes by the participants, and the data will be verified for accuracy and completion by the investigator or delegate during regularly scheduled interactions with the participant. Thus, the EPD will be considered the source for these data.

For each self-administered injection of Jivi, information must be recorded on the EPD as follows:

Each injection of Jivi:

a. Date and time
b. Injection record
c. Individual vial number (bar code scan from vial label or manual entry) and units administered
d. Reason for treatment

   Prophylaxis
   Spontaneous bleed first treatment
   Trauma bleed first treatment
   Follow-up treatment
   Other

Injections of Jivi as part of protocol mandated visits and procedures will be recorded on the respective CRF pages.

All bleeding episodes (regardless if treated or not, or treated at home or under medical supervision) as well as any potential treatment with other hemophilia drugs will be recorded in the EPD:

Bleeding episode (onset)

a. Date and time of onset
b. Type of bleed (spontaneous, trauma; joint, muscle, skin/mucosal, internal, other)
c. Location
d. Intensity (mild, moderate, severe)
e. Treated [yes/no];

   if "yes": Date and time
   Product used: Jivi or other
   Doses

If Jivi is used for the treatment of a bleeding episode, the response to treatment (excellent, good, moderate, poor, too early to tell) must to be recorded

For guidance to the participant, the following definitions for response to treatment are suggested:

Excellent: Abrupt pain relief and/or improvement in signs of bleeding with no additional injection administered

Good: Definite pain relief and/or improvement in signs of bleeding, but possibly requiring more than one injection for complete resolution

Moderate: Probable or slight improvement, with at least one additional injection for complete resolution

Poor (or None): No improvement or condition worsens.

8.1.2 Incremental Recovery of Jivi

Blood samples for Jivi trough (predose) and recovery levels (15-30 min post injection) will be collected in all participants. Incremental recovery will be determined by collecting a sample for FVIII level before the scheduled injection, and a second sample collected 15-30 min after end of the injection. The exact sampling times before and after injection and the dose administered will be documented in the CRF. Incremental recovery of Jivi is determined by measuring FVIII activity.

Injections given at study visits will be recorded in the site participant records, which will be the source documents and will be used to enter this information in the CRF.

The samples will be collected as described in detail in the laboratory manual. All samples will be processed in the central laboratory. Plasma concentrations of FVIII will be measured using a validated FVIII activity assay ("chromogenic assay").

Samples for incremental recovery should be collected on days when the next prophylactic injection is scheduled and at least 72 h after the prior injection has been given. The measurements should only be performed when the participant is not actively bleeding.

Recoveries should be performed using the participants assigned treatment dose, rounded to full vial size.

Samples will be collected at Baseline, Visit 3 (Week 8-10), and Last Visit, or in case of suspicion of loss of efficacy (LoE)/hypersensitivity and at additional time points based on the investigator's discretion.

8.1.3 Activity Tracker

CCI [redacted]

8.2 Safety Assessments

Planned time points for all safety assessments are provided in the SoA.

The safety endpoints for the study include:

Primary Endpoints throughout the study:

- FVIII inhibitor development by the Nijmegen Bethesda assay. Any positive inhibitor test will be confirmed by testing a second separately drawn sample in a central laboratory

Secondary Endpoints throughout the study:

- TEAE.
- Treatment-emergent anti-drug antibodies (ADA) against Jivi and Anti-PEG antibodies at the same time points as the FVIII inhibitor tests and in case of clinical suspicion of LoE/Hypersensitivity

8.2.1 Measurements of Immunogenicity

All participants will be tested for immunogenicity at Screening, Baseline (Day 1), Visit 3, Visit 4, Visit 5, and Last Visit, or in case of suspicion of LoE/hypersensitivity.

Antibodies to Jivi and/or PEG (ADA)

Binding antibodies to Jivi and/or PEG are analyzed in an enzyme-linked immunosorbent assay (ELISA) Type screening ADA assay using Jivi. Positive screened samples will be characterized for specificity of the antibody response against Jivi and/or against PEG and for their neutralizing activity.

FVIII inhibitor

FVIII inhibitor testing will be done according to the Nijmegen modified Bethesda assay. A positive inhibitor test is defined with a threshold of ≥0.6 BU at the central laboratory.

If an inhibitor is detected as part of scheduled testing, the investigator will to be notified. Repeat testing within 2 to 4 weeks of notification should to be obtained. Any positive test will be confirmed by a second different sample. Only after confirmation of the positive result, the inhibitor has to be reported as SAE.

Loss of Efficacy (LoE)/Hypersensitivity reaction

In case loss of efficacy is suspected by the investigator (ie, measured by low FVIII levels, poor recovery, and unexpected clinical symptoms of bleeding or no response to treatment of a bleed) or the participant presents symptoms of an hypersensitivity reaction, plasma samples will be tested for FVIII inhibitor and ADA, and positive screened samples will be further characterized for specificity of the antibody response against Jivi and/or against PEG. Samples that confirmed positive against Jivi will be further analyzed in a modified Nijmegen Bethesda assay for inhibitory activity against Jivi.

In addition to this, incremental recovery following administration of Jivi will be measured. Samples for Jivi trough and recovery levels following an injection of Jivi will be collected when loss of efficacy is suspected (See Section 8.1.2). In case of a slightly reduced recovery (compared to previous product or below 1.5 IU/dl per IU/kg), the recovery should be repeated locally after the next injection.

A clinical immune response manifested as symptoms of acute hypersensitivity and/or loss of drug effect has been observed primarily in children < 6 years, within the first 4 exposure days, which was associated with anti-PEG antibodies. CCI [redacted] in such cases Jivi should be discontinued, participants should switch to a previously effective factor VIII product, and the recovery should be measured locally after injection of the previous FVIII which will be normal in these cases, ruling out an inhibitor.

8.2.2 Physical Examinations

- Physical examinations will be performed at Screening and End of Study/Early Termination Visit.

- A complete physical examination will include, at a minimum, assessments of the general appearance, dermatologic, head, eyes, ears, nose, mouth/throat/neck, thyroid, lymph nodes, cardiovascular, respiratory, gastrointestinal extremities, neurological and musculoskeletal and review of systems. Height and weight will also be measured and recorded.
- Body weight will be measured every 6 months (Visits 4, 5, and 6).
- Investigators should pay special attention to clinical signs related to previous serious illnesses. Any abnormal finding should be documented.

8.2.3 Vital Signs

- Vital signs will be measured at Screening, Baseline, and End of Study/Early Termination Visit. In case of any in-hospital injection related AE, vital signs will be measured post-injection for participants.
- Heart rate, respiratory rate, and systolic and diastolic blood pressure will be assessed.
- Blood pressure and heart rate measurements should be preceded by at least 5 minutes of rest for the participant in a supine or seated position without distractions (e.g., television, cell phones).

8.2.4 Clinical Safety Laboratory Assessments

- See Section 10.2 for the list of clinical laboratory tests to be performed and to the SoA for the timing and frequency.
- The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the CRF. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.
- All laboratory tests with values considered clinically significantly abnormal during participation in the study should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the investigator.
    - If such values do not return to normal/baseline within a period of time judged reasonable by the investigator, the etiology should be identified and the sponsor notified.
    - All protocol-required laboratory assessments, as defined in Section 10.2, must be conducted in accordance with the laboratory manual and the SoA.
    - If laboratory values from non-protocol specified laboratory assessments performed at the institution’s local laboratory require a change in participant management or are considered clinically significant by the investigator (e.g., SAE or AE or dose modification), then the results must be recorded in the CRF.

8.3 Adverse Events and Serious Adverse Events

The definitions of an AE or SAE can be found in Section 10.3.

AE will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative or health care professional not involved in the study).

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE. They remain responsible for following up SAEs, or AEs considered related to the study intervention or study procedures, or those that caused the participant to discontinue the study. Events of Special Interest have to be followed up regardless of causality or relationship to study intervention (see Section 8.3.7).

8.3.1 Time Period and Frequency for Collecting AE and SAE Information

All AEs and SAEs will be collected from the signing of the informed consent form (ICF) until the end of the final study visit at the time points specified in the SoA (Section 1.3).

Medical occurrences that begin before obtaining informed consent but are diagnosed at screening or during the screening period (e.g., abnormal lab values) will be recorded on the Medical History/Current Medical Conditions section of the case report form (CRF), not the AE section.

All SAEs will be recorded and reported to the sponsor or designee immediately and under no circumstances should this exceed 24 hours, as indicated in Section 10.3. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.

Investigators are not obligated to actively seek AE or SAE after conclusion of the study participation. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he considers the event to be reasonably related to the study intervention or study participation, the investigator must promptly notify the sponsor.

8.3.2 Method of Detecting AEs and SAEs

The method of recording, evaluating, and assessing causality of AE and SAE and the procedures for completing and transmitting SAE reports are provided in Section 10.3.

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the participant is the preferred method to inquire about AE occurrences.

8.3.3 Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs and non-serious AEs of special interest (as defined in Section 8.3.7, will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3). Further information on follow-up procedures is given in Section 10.3.3.

8.3.4 Regulatory Reporting Requirements for SAEs

- Prompt notification by the investigator to the sponsor of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.
- The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards (IRB)/Independent Ethics Committees (IEC), and investigators.
- Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.
- An investigator who receives an investigator safety report describing an SAE or other specific safety information (e.g., summary or listing of SAEs) from the sponsor will review and then file it along with the Investigator's Brochure and will notify the IRB/IEC, if appropriate according to local requirements.

8.3.5 Pregnancy

Contraception Guidance

- It has been shown that there is no target-related specific transport mechanism for Jivi into semen or from semen into the conceptus. Following administration to a male participant, Jivi would not be bioavailable via seminal delivery to the developing conceptus of an untreated partner. Therefore, no method of contraception is needed.

Collection of Pregnancy Information

- Bayer usually does not gather pregnancy information of drug exposure via father; however, if those cases are reported, details of all pregnancies in female partners of male participants will be collected after the start of study intervention and until one week period that is at least 5 terminal half-lives after the last dose.
- If a pregnancy is reported, the investigator should inform the sponsor of learning of the pregnancy.

8.3.6 Disease-Related Events and/or Disease-Related Outcomes Not Qualifying as AEs or SAEs

The following disease related outcome is common in participants with hemophilia A and can be serious/life threatening:

- Bleeding event

Any bleeding event, regardless if treated or not, occurring during the study will not be documented as an AE, because this is captured in the assessment of efficacy.

Because these events are typically associated with the disease under study, they will not be reported according to the standard process for expedited reporting of AEs. These events will be recorded in the EPD.

NOTE: However, if the bleed fulfills the criterion for an SAE (e.g. results in hospitalization), then the event should be recorded and reported as an SAE (see Section 10.3.2).

8.3.7 Events of Special Interest

Hypersensitivity reactions are a known and listed adverse drug reactions for FVIII products and have been reported with use of Jivi. Loss of efficacy of the drug product has also been reported in children < 6 years of age and may be associated with the development of antibodies to PEG. All such reported events occurred early in treatment, within the first 4 ED. Both of these events are defined in this study as adverse events of special interest and must be reported as adverse events.

In the event of such a hypersensitivity reaction or reported loss of efficacy of the treatment product, antibody and inhibitor testing will be obtained. Loss of efficacy needs to be documented by pre and post factor VIII levels around an injection of the Jivi, using appropriate laboratory measures, and be confirmed in the central laboratory.

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8.4 Treatment of Overdose

Sponsor does not recommend specific treatment for an overdose.

8.5 Pharmacokinetics

PK parameters are not evaluated in this study.

8.6 Pharmacodynamics

Pharmacodynamic parameters are not evaluated in this study.

8.7 Genetics

Genetics parameters are not evaluated in this study.

8.8 Biomarkers

Biomarkers for renal safety will be evaluated in the study (see Section 10.2 Appendix 2).

8.9 Other investigations

CCI [redacted]

CCI [redacted]

CCI [redacted]

8.10 Health Economics OR Medical Resource Utilization and Health Economics

Health Economics/Medical Resource Utilization and Health Economics parameters are not evaluated in this study.

9. Statistical Considerations

9.1 Statistical Hypotheses

The study is not designed to test any predefined hypothesis. All analyses will be descriptive or exploratory.

9.2 Sample Size Determination

Descriptive statistics will be used. The sample size is defined by the Note for guidance on the clinical investigation of recombinant FVIII products in order to fulfill post-marketing requirements. During the clinical development program, a total of 232 participants were included in the Phase 1 and 2/3 clinical development program. Among these participants, 168 participants achieved >100 ED, and additional 17 participants achieved 50-100 ED. It is considered, that at least additional 25 participants would support the assessment of general safety and efficacy as required by guidelines EMA/CHMP/BPWP/144533/2009 rev.2 (EMA 2017).

A pooled analysis will be performed for all patients included in the Phase III and IV studies. The following trials will be included in the pooled analysis:

Study	Total number of participants included
PROTECT VIII	134
PROTECT Kids	73
Planned Phase IV study	≥25
Expected total	≥232

Assessment of safety will be done for the safety population including all participants with at least 1 injection of Jivi. Assessment of efficacy will be performed for the ITT population including participants with diary/injection data available.

9.3 Populations for Analyses

For purposes of analysis, the following populations are defined:

Population	Description
Enrolled	All participants who sign the ICF
Safety population for the study 19764	Participants enrolled into the study and received at least 1 dose of study intervention. Participants will be analyzed according to the intervention they actually received. The safety population will be used for the safety analysis.
Intent-to-treat (ITT) population for the study 19764	All safety participants who have injection/bleeding data from the EPD and CRF for at least 3 months. The ITT population will be used for the efficacy analysis.
Safety population for pooled analysis	The safety population for the pooled analysis will consist of the safety population of this study as defined above and the safety populations of studies 13024 Part A and 15912.
Efficacy population for pooled analysis	The efficacy population for the pooled analysis will consist of the ITT population of this study as defined above and the extension ITT populations of studies 13024 Part A and 15912.

9.4 Statistical Analyses

The statistical analysis plan will be developed and finalized before first patient first visit (FPFV) and will describe the participant populations to be included in the analyses, and procedures for accounting for missing, unused, and spurious data. This section is a summary of the planned statistical analyses of the primary and secondary endpoints.

9.4.1 Efficacy Analyses

The secondary objective of the study is to assess clinical efficacy. All efficacy analyses will be performed on the ITT population with a treatment period of at least 3 months.

The following efficacy variables will be analyzed:

- Annualized bleeding rate for joint and spontaneous bleeds
- Percentage of participants with 0 spontaneous bleeds within a 6-months treatment period
- Annualized number of total bleeds (sum of spontaneous bleeds and trauma bleeds)
- Incremental recovery will be summarized
- Total number of exposure per year will be documented in patient diaries and summarized
- Extent of exposure to study intervention during the study in terms of exposure days (ED) and injection characteristics (number of units, consumption dose/kg per participant/year, reason for treatment, type, location and severity of bleeds and response to treatment) will be summarized for each participant receiving any amount of drug.

Other pre-specified exploratory endpoints will be described in the statistical analysis plan finalized before database lock.

An integrated efficacy analysis will be done based on combined data from this study and studies 13024 Part A and 15912. Results will be provided by age groups.

9.4.2 Safety Analyses

All safety analyses will be performed on the Safety Population. Laboratory findings, adverse events, concomitant medications, vital signs, and medical history data will be provided in subject listings.

Those participants who were given at least one dose of Jivi will be valid for the safety analysis. Inhibitor development will be summarized by time point and presented in subject listings. The purpose of the listing is to delineate the clinical factors which may be positively associated with development of the inhibitor. Confirmation of positive inhibitor titers (Bethesda ≥0.6 BU/mL) will require repeat measurement. If the repeated inhibitor result is <0.6 BU without intervention, the inhibitor is not confirmed and should not be reported as an SAE. Inhibitors will be classified as being either low titer (≥0.6 BU/mL and ≤5 BU/mL) or high titer based upon persistence of an inhibitor >5 BU. Participants will also be monitored for other antibodies against the drug substance Jivi and/or PEG. Proportions of participants with inhibitor or antibodies will be presented in an overview table.

Laboratory values and vital signs will be summarized. Individual listings of AEs (including AEs as reported, start, duration, severity, relation to study drug) will be provided. The incidence of treatment-emergent adverse events (AEs) will be summarized using the Medical Dictionary for Regulatory Activities (MedDRA). An AE will be considered treatment-emergent if it starts after first injection and not later than 7 days after last injection of Jivi.

Integrated safety analyses will be done based on combined data from this study and studies 13024 Part A and 15912. Summary tables for demographics, baseline characteristics (including gene defect), medical history (including family history of hemophilia and history of inhibitor), concomitant medications, extent of exposure, treatment-emergent AEs, and laboratory findings will be provided. Results will be provided by age groups.

9.5 Interim Analyses

An optional interim analysis will be performed, if needed for regulatory submission or publication purposes, after all participants have been treated for 6 months for assessment of the main safety (inhibitor development) and efficacy endpoints. The risk for inhibitor development is highest during the first 20-50 ED. After this timepoint, the study would be continued according to the study design and protocol.

10. Supporting Documentation and Operational Considerations

10.1 Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1 Regulatory and Ethical Considerations

- This study is a post-approval regulatory requirement according to the EMA Guidelines for a new marketed FVIII and will be conducted in accordance with the protocol and with the following:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
  - Applicable International Council for Harmonization (ICH) Good Clinical Practice (GCP) Guidelines
  - Applicable laws and regulations
- The protocol, protocol amendments, ICF, SmPC, and other relevant documents (e.g., advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- The investigator will be responsible for the following:
  - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
  - Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
  - Providing oversight of the conduct of the study at the site and adherence to requirements of ICH guidelines, the IRB/IEC, and all other applicable local regulations

10.1.2 Financial Disclosure

Investigators and sub-investigators directly involved in the treatment or evaluation of study participants will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

10.1.3 Informed Consent Process

- The investigator and/or delegate will explain the nature of the study to the participant and answer all questions regarding the study, based on the patient informed consent. The patient informed consent will contain all relevant information on the study.
- Participants must be informed that their participation is voluntary. Participants will be required to sign a statement of informed consent that meets the requirements of local regulations, ICH guidelines, where applicable, and the IRB/IEC or study center.
- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Participants must be re-consented to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the participant.

Participants who are rescreened are required to sign a new ICF.

10.1.4 Data Protection

- Participants will be assigned a unique identifier by the sponsor. Any participant records or datasets that are transferred to the sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.
- The participant must be informed that his personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant.
- The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

10.1.5 Dissemination of Clinical Study Data

Result Summaries of Bayer's sponsored clinical trials in drug development phases II, III and IV and Phase I studies in patients are provided in the Bayer Trial Finder application after marketing authorization approval in line with the position of the global pharmaceutical industry associations laid down in the "Joint Position on the Disclosure of Clinical Trial Information via Clinical Trial Registries and Databases". In addition results of clinical drug trials will be provided on the publicly funded website www.ClinicalTrials.gov and EU Clinical Trials Register in line with the applicable regulations.

Bayer commits to sharing upon request from qualified scientific and medical researchers patient-level clinical trial data, study-level clinical trial data, and protocols from clinical trials

in patients for medicines and indications approved in the United States (US) and European Union (EU) on or after January 01, 2014 as necessary for conducting legitimate research.

All Bayer-sponsored clinical trials are considered for publication in the scientific literature irrespective of whether the results of the clinical trials are positive or negative.

10.1.6 Data Quality Assurance

- All participant data relating to the study will be recorded on electronic CRF unless transmitted to the sponsor or designee electronically (e.g., laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.
- The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.
- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- Monitoring details describing strategy (e.g., risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the Monitoring Plan.
- The sponsor or designee is responsible for the data management of this study including quality checking of the data.
- The sponsor assumes accountability for actions delegated to other individuals (e.g., Contract Research Organizations).
- Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator for 15 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

10.1.7 Source Documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.
- Data reported in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.
- Definition of what constitutes source data can be found in a source document checklist.
- Patient reported outcome variables which are transmitted via EPD are considered source documentation.

10.1.8 Study and Site Closure

The sponsor designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the sponsor or investigator may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the sponsor's procedures, or GCP guidelines
- Inadequate recruitment of participants by the investigator
- Discontinuation of further study intervention development

10.1.9 Publication Policy

- The results of this study may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to the sponsor before submission. This allows the sponsor to protect proprietary information and to provide comments.
- The sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.
- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

10.2 Appendix 2: Clinical Laboratory Tests

- The tests detailed in Table 10–1 will be performed by the central laboratory
- All laboratory analyses will be performed at central laboratories. Investigators will be provided with a laboratory manual for instructions on how to collect and process samples.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5 of the protocol.
- Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations locally or centrally as needed.

Table 10–1: Protocol-Required Safety Laboratory Assessments

Laboratory Assessments	Parameters			
Hematology	Platelet Count	White blood cell (WBC) count with Differential		
	Erythrocytes			
	Hemoglobin			
	Hematocrit			
Clinical Chemistry	Blood urea nitrogen (BUN)	Potassium	Aspartate Aminotransferase (AST)	Total bilirubin
	Creatinine	Sodium	Alanine Aminotransferase (ALT)	Total Protein
	Albumin			
Routine Urinalysis	• pH, glucose, protein, blood, ketones, bilirubin, urobilinogen, leukocyte esterase by dipstick			
Renal Biomarkers	• The urine samples for assessment of renal safety in participants with long term polyethylene glycol (PEG) exposure will include biomarkers (e.g. total protein and albumin [as albumin/creatinine ratio], and potentially beta-2microglobulin and Kim-1)			
Other Laboratory Tests	• Serology: HIV antibody for screening purpose only • Immunogenicity testing including antibodies to Jivi and/or PEG and FVIII inhibitor. • FVIII level • PEG level in plasma All routine study-required laboratory assessments will be performed by a central laboratory, with the exception of some samples sent by central lab to independent specialty labs for required tests of FVIII level, FVIII inhibitors, antibodies to Jivi and/or PEG (anti-drug antibodies [ADA]) and PEG			

Investigators must document their review of each laboratory safety report.

10.3 Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.3.1 Definition of AE

AE Definition

In a clinical study, an AE is any untoward medical occurrence (ie, any unfavorable and unintended sign [including abnormal laboratory findings], symptom or disease) in a subject or clinical investigation subject after providing written informed consent for participation in the study. Therefore, an AE may or may not be temporally or causally associated with the use of a medicinal (investigational) product.

A surgical procedure that was planned prior to the start of the study by any physician treating the subject should not be recorded as AE (however, the condition for which the surgery is required may be an AE).

In the following differentiation between medical history and AEs, the term "condition" may include abnormal, eg, physical examination findings, symptoms, diseases, laboratory values.

- Conditions that started before signing of informed consent and for which no symptoms or treatment are present until signing of informed consent are recorded as medical history (eg, seasonal allergy without acute complaints, abnormal laboratory finding at screening).
- Conditions that started before signing of informed consent and for which symptoms or treatment are present after signing of informed consent, at unchanged intensity, are recorded as medical history (eg, allergic pollinosis).
- Conditions that started or deteriorated after signing of informed consent will be documented as adverse events.

Note: Any bleeding event occurring during the study will not be documented as an AE, because this event is captured in the assessment of efficacy. However, if the bleed requires hospitalization or fulfills another seriousness criterion, it must be reported as a Serious Adverse Event (SAE) (Section 10.3.2).

Bleeding events treated with Jivi and recorded in the EPD do not need to be documented as AEs because they are already captured. However, occurrence of traumatic injury and other bleeds should follow standard AE reporting procedures. Any bleed requiring hospitalization or fulfilling another seriousness criterion must be reported as a SAE (Section 10.3.2).

Events Meeting the AE Definition

- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.
- The signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfil the definition of an AE or SAE. Also, "lack of efficacy" or "failure of expected pharmacological action" also constitutes an AE or SAE.

Events NOT Meeting the AE Definition

- Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.
- The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition.
- Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the procedure is the AE.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.
- Any bleeding event occurring during the study will not be documented as an AE, because this is captured in the assessment of efficacy. However, if the bleed fulfills the criterion for an SAE (e.g. results in hospitalization), then the event should be recorded and reported as an SAE.

10.3.2 Definition of SAE

An SAE is defined as any untoward medical occurrence that, at any dose:

a. Results in death

b. Is life-threatening

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

c. Requires inpatient hospitalization or prolongation of existing hospitalization

A hospitalization or prolongation of hospitalization will not be regarded as an SAE if at least one of the following exceptions is met:

- The admission results in a hospital stay of less than 12 hours
- The admission is pre-planned
  (ie, elective or scheduled surgery arranged prior to the start of the study)
- The admission is not associated with an AE
  (eg, social hospitalization for purposes of respite care).

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

d. Results in persistent disability/incapacity

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.
- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect

f. Is another medically important serious event as judged by the investigator.

- Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.
- Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

10.3.3 Recording and Follow-Up of AE and/or SAE

AE and SAE Recording

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (e.g., hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The investigator will then record all relevant AE/SAE information in the CRF.
- It is not acceptable for the investigator to send photocopies of the participant's medical records to Study Monitor/Medical Monitor in lieu of completion of the AE/SAE CRF page.
- There may be instances when copies of medical records for certain cases are requested by the Sponsor. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to the Sponsor.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

- The investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to 1 of the following categories:
- Mild: An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities.
- Moderate: An event that causes sufficient discomfort and interferes with normal everyday activities.
- Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with an SAE. Severe is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe.
- An event is defined as 'serious' when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

Assessment of Causality

- The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated.

- The investigator will also consult the Investigator's Brochure (IB) and/or Product Information, for marketed products, in his/her assessment.
- For each AE/SAE, the investigator **must** document in the medical notes that he has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred, and the investigator has minimal information to include in the initial report to the Sponsor. However, **it is very important that the investigator always make an assessment of causality for every event before the initial transmission** of the SAE data to the Sponsor.
- The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AEs and SAEs

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the Sponsor to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- New or updated information will be recorded in the originally completed CRF.
- The investigator will submit any updated SAE data to the Sponsor within 24 hours of receipt of the information.

10.3.4 Reporting of SAEs

SAE Reporting to the Sponsor via an Electronic Data Collection Tool

- The primary mechanism for reporting an SAE will be the electronic data collection tool.
- If the electronic system is unavailable, then the site will use the paper SAE data transmission (see next section) in order to report the event within 24 hours.
- The site will enter the SAE data into the electronic system as soon as it becomes available.
- After the study is completed at a given site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information on a paper SAE form (see next section) or to the Sponsor's Medical Monitor by telephone.
- Contacts for SAE reporting can be found in the investigator Site File.

SAE Reporting to the Sponsor via Paper CRF

- Email transmission of the SAE paper CRF is the preferred method to transmit this information to the Sponsor´s Medical Monitor.
- In rare circumstances and if email transmission is not feasible, notification by telephone is acceptable with a copy of the SAE data collection tool sent by overnight mail or courier service.
- Initial notification via telephone does not replace the need for the investigator to complete and sign the SAE CRF pages within the designated reporting time frames.
- Contacts for SAE reporting can be found in the investigator Site File.

10.4 Appendix 4: Visit Description

10.4.1 Visit 1 – Screening (Approximately 2 to 8 Weeks)

Screening may take place over multiple site visits. At the Screening Visit, the following procedures and assessments will be performed:

- Obtain signed informed consent from participants
  Note: No screening procedures should be performed unless written informed consent has been obtained
- Allocation of a unique participant number
- Review of eligibility requirements; no participant should receive study intervention unless all inclusion and exclusion criteria are met listed in Section 5.1 and 5.2. Confirmation of selection criteria may be based on medical records for some conditions, but laboratory test results must be available for the listed items to confirm eligibility.
- Collect demographic data (age, sex [male only], race, ethnicity, and gene defect)
- Full physical examination including neurological standard assessment, height, and weight
- Collect information on activity level (type of sports, hrs/wk)
- Obtain a complete medical and surgical history (general, disease, family history of hemophilia, and history of inhibitor development)
  - Include any information on cardiovascular risk, hepatic disease, renal impairment, prior use of PEGylated medications (e.g., PEG- interferon, PEG-anti- tumor necrosis factor [TNF])
  - Specific information on history of hemophilia (date of diagnosis, start of therapy, prior and current factor VIII products, number of ED, type of factor VIII gene

mutation (from history), family history, FVIII level, family and personal history of past inhibitor formation, current treatment product and regimen, number and type of bleeds in the last 12 months, and presence and location of target joints.) If available, data on prior PK with the participants' previous FVIII product will be collected (e.g. recovery and half-life).

- Collect information on previous medication (medication history)
- Vital signs (Heart rate, respiratory rate, and blood pressure; see Section 8.2.3)
- Urine sample (routine urinalysis and renal biomarkers; see Table 10–1)
- Blood samples for (see details in Table 10–1):
  - Laboratory evaluation (hematology and clinical chemistry)
  - HIV screening (in case negative result in patient documentation is older than 1 year at date of screening)
  - CD 4+ cell count (only if participant is HIV positive)
  - Immunogenicity testing
  - PEG level in plasma
- Training on and dispense of EPD devices
- Training and dispense of activity tracker; ask the participant to wear activity tracker for continuous 2-3 weeks after screening before Baseline Visit (see Section 8.1.3)
- Concomitant medication review
- AE review

10.4.2 Visit 2 – Baseline Predose (Day 1)

This visit will be serving as the Baseline Visit; it will include the first administration of study intervention. The Baseline Visit should take place within 2 to 8 weeks after Screening Visit and at least 72 hour after last FVIII product administration.

This visit should start with the following assessments:

- Confirmation of eligibility including check of laboratory test results
  Note: Participants must have negative results from the central laboratory for inhibitory antibodies against FVIII (< 0.6 BU determined with the Nijmegen modified Bethesda assay)

Thereafter, the following procedures and assessments will be performed and data recorded:

- Remind the participants to wear the activity tracker for 2-3 continuous weeks after the start of treatment before Visit 3
- Concomitant medication review
- AE review
- Vital signs (Heart rate, respiratory rate, and blood pressure; see Section 8.2.3)

- Urine sample (routine urinalysis and renal biomarkers; see Table 10–1)
- Blood sample collection **before** administration of study intervention
  - Blood samples for:
    - Immunogenicity testing
    - Incremental recovery of Jivi
- In-hospital injection of Jivi
- Procedures and sample collection **after** administration of study intervention
  - Blood samples for:
    - Incremental recovery of Jivi (15-30 min after end of injection; see Section 8.1.2)
  - In case of any injection related AE at site, vital signs will be collected
- Dispense study intervention for home injections in accordance with IxRS drug dispensing schedule
- Instruction on the treatment regimen to be administered to the participant
- Check of EPD entries and bleeding history
- Begin regular monthly contact between participant and the site to check EPD documentation and AE review until the End of Study/Early Termination

10.4.3 Visit 3 – ED 10-15 (Week 8-10)

This visit should take place at least 72 hours after the last injection of Jivi.

- Dose regimen adjustment
- Blood sample collection **before** administration of study intervention:
  - Immunogenicity testing
  - Incremental recovery of Jivi
- In-hospital injection of Jivi
- Procedures and blood sample collection **after** administration of study intervention
  - Incremental recovery of Jivi (15-30 min after end of injection; see Section 8.1.2)
  - In case of any injection related AE at site, vital signs will be measured
- Concomitant medication review
- AE review
- Check of EPD entries and bleeding history
- Dispense study intervention for home injections in accordance with IxRS drug dispensing schedule

- Return used and unused study intervention
- Continue regular monthly contact between participant and the site to check EPD documentation and AE review until the End of Study/Early Termination

10.4.4 Visit 4 – ED 50-75 (Month 6 ± 14 days)

This visit should take place approximately 48 or 72 hours (if not possible then 96 hours) after the last injection of Jivi.

- Ask the participant to wear activity tracker for continuous 2-3 weeks after Visit 4 (Month 6) before Visit 5 (Month 12)
- Body weight measurement
- Concomitant medication review
- AE review
- Blood samples for (see details in Table 10–1):
  - Immunogenicity testing
  - FVIII level
- Dispense study intervention for home injections in accordance with IxRS drug dispensing schedule
- Return used and unused study intervention
- Check of EPD entries and bleeding history
- Continue regular monthly contact between participant and the site to check EPD documentation and AE review until the End of Study/Early Termination

10.4.5 Visit 5 – ED 50-75 (Month 12 ± 14 days)

This visit should take place approximately 48 or 72 hours (if not possible then 96 hours) after the last injection of Jivi.

- Body weight measurement
- Concomitant medication review
- AE review
- Urine sample (routine urinalysis and renal biomarkers; see Table 10–1)
- Blood samples for (see details in Table 10–1):
  - Laboratory evaluation (hematology and clinical chemistry)
  - Immunogenicity testing
  - FVIII level

- Dispense study intervention for home injections in accordance with IxRS drug dispensing schedule
- Return used and unused study intervention
- Check of EPD entries and bleeding history
- Documentation of activity tracker; return activity tracker
- Continue regular monthly contact between participant and the site to check EPD documentation and AE review until the End of Study/Early Termination

10.4.6 Visit 6 if needed – ED 50-75 (Month 18 ± 14 days)

- Body weight measurement
- Concomitant medication review
- AE review
- Dispense study intervention for home injections in accordance with IxRS drug dispensing schedule
- Return used and unused study intervention
- Check of EPD entries and bleeding history
- Continue regular monthly contact between participant and the site to check EPD documentation and AE review until the End of Study/Early Termination

10.4.7 Last Visit – ED 100 (End of Study/Early Termination + 14 days)

This visit should take place at least 72 hours after the previous injection of Jivi.

The following procedures and assessments will be performed in participants reach ED 100 or at the time of premature termination:

- Concomitant medication review
- AE review
- Full physical examination including neurological standard assessment, height, and weight
- Vital signs (Heart rate, respiratory rate, and blood pressure; see Section 8.2.3)
- Urine sample (routine urinalysis and renal biomarkers; see Table 10–1)
- Laboratory evaluation (hematology and clinical chemistry)
- PEG level in plasma
- Blood sample collection **before** administration of study intervention
    - Immunogenicity testing

  - Incremental recovery of Jivi
- In-hospital injection of Jivi
- Procedures and blood sample collection **after** administration of study intervention
  - Incremental recovery of Jivi (15-30 min after end of injection; see Section 8.1.2)
  - In case of any injection related AE at site, vital signs will be measured
- Return used and unused study intervention
- Check of EPD entries and bleeding history and return EPD
- Return activity tracker in case of early termination before Visit 5

10.5 Appendix 5: Abbreviations

ABR	Annualized bleeding rate
ADA	Anti-drug antibodies
AE	Adverse event
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AUC	Area under the curve
BDD	B-domain deleted
BU	Bethesda unit
CD4	Cluster of differentiation 4 (CD4 receptor)
COX	Cyclooxygenase
CRF	Case Report Form (either paper or electronic)
ED	Exposure day
e.g.	exempli gratia, for example
EHL	Extended half-life
EMA	European Medicines Agency
EPD	Electronic patient diary
EU	European Union
FDA	US Food and Drug Administration
FVIII	Human coagulation factor VIII
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
HIV	Human Immunodeficiency Virus
IB	Investigator's Brochure
ICF	Informed consent form
ICH	International Council for Harmonization
ie	Id est, that is
IEC	Independent Ethics Committee
IMP	Investigational medicinal product
IRB	Institutional Review Board
ITT	Intent to treat
IU	International units
IV	Intravenous
IxRS	Interactive voice/web response system
Kg	Kilogram
LoE	Loss of efficacy
LPLV	Last participant last visit
MedDRA	Medical Dictionary for Regulatory Affairs
NIMP	Non investigational medicinal product
PEG	Polyethylene glycol
PK	Pharmacokinetic
PMDA	Pharmaceuticals and Medical Devices Agency
PMI	Post-marketing investigation

PTP	Previously treated patients
QoL	Quality of Life
rFVIII	Recombinant factor VIII
SAP	Statistical analysis plan
SAE	Serious Adverse Event
SmPC	Summary of Product Characteristics
SoA	Schedule of activities
SUSAR	Suspected unexpected serious adverse reaction
$t_{1/2}$	Half-life
TEAE	Treatment-emergent adverse event
WHO	World Health Organization

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