Document Type:	Study protocol
Official Title:	A multi-center, pediatric phase III, non-controlled, open-label trial to evaluate the safety of BAY 94 9027 for prophylaxis and treatment of bleedings in previously Treated Patients aged 7-<12 years with severe hemophilia A
NCT Number:	NCT05147662
Document Date:	06-Apr-2023

Title Page

Protocol Title:

A Phase 3, single-group treatment, open-label, study to evaluate the safety of BAY 94-9027 infusions for prophylaxis and treatment of bleeding in previously treated children aged 7 to <12 years with severe hemophilia A

Protocol Number:	21824
Protocol Version:	3.0
Amendment Number:	2
Amendment Scope:	Global
Compound Number:	Damoctocog alfa pegol (Jivi®), BAY 94-9027
Short Title:	A Phase 3 safety study of BAY 94-9027 in children 7 to <12 years of age with severe hemophilia A
Study Phase:	3
Acronym:	Alfa-PROTECT
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 no.: 2021-004858-30

EU CT no.: 2023-504388-18-00

Protocol Date: **06 APR 2023**

Name: PPD Role: PPD

This is an electronically generated document that does not bear any sponsor signatures. The signature of the sponsor's medically responsible person is filed in the TMF and available on request.

Medical Monitor name and contact information will be provided separately.

Document History Table

DOCUMENT HISTORY			
Document	**Version**	**Date**	**Comments (if applicable)**
Amendment 2 (Global)	3.0	06 APR 2023	
Amendment 1 (Global)	2.0	25 MAY 2022	
Clinical Study Protocol	1.0	17 SEP 2020	Version approved by Health Authorities

Protocol Amendment Summary of Changes Table

Amendment 2 (06 APR 2023)

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC and Article 2(2)(13) of the REGULATION (EU) No 536/2014 of the European Parliament and the Council of the European Union.

Overall Rationale for the Amendment:

Immunogenicity to the PEG moiety in Jivi is age related. Preliminary data from the initial patients dosed in this study indicate that when an immune response occurs, it is less severe in this age group than that typically observed in younger children 2-5 years of age. This reduced immune response has been characterized by low titers of anti-PEG antibodies (1:1 to 1:4) with mild to moderate reductions in FVIII recovery during EDs 2-4. Continued dosing with Jivi has demonstrated decreased levels of anti-PEG antibodies and improved FVIII recovery.

The original protocol specifies that local FVIII recovery measurements are performed at the clinical site based on the investigator's discretion or when there is suspicion of reduced recovery. To better protect study participants against the potential for a bleed related to lower-than-expected FVIII levels, this amendment recommends routine local FVIII recovery measurements be performed at the clinical site for the first 4 EDs. This more standardized approach will enable the treating clinician to adjust the dose and dosing interval for the subsequent EDs.

Section # and Name	Description of Change	Brief Rationale
Title Page	GCL name change	Updated to reflect current team responsibilities
	EU CT number added	Added in compliance with EU CTR
Document History Table	Current amendment added	
Protocol Amendment Summary of Changes Table	Updated to reflect changes implemented in current amendment	
1.3 Schedule of Activities (SoA)	Laboratory chemistry added at Visit 2	Correction for consistency between SoA and rest of protocol
	Guidance for FVIII recovery added to footnotes	Age-appropriate frequency of FVIII recovery level assessment will reduce the potential for bleeds and improve clinician management of study drug.
2.1 Study Rationale 2.2 Background 3 Objectives, Endpoints, and Estimands 8.3.8 Adverse Events of Special Interest	Age range for children in whom an immune response to anti-PEG antibodies in the first 4 EDs updated	Change made for consistency throughout the protocol
2.2 Background	Description of immunogenicity to PEG and appropriate assessment of FVIII recovery levels in study participants added to section	Age-appropriate frequency of FVIII recovery level assessment will reduce the potential for bleeds and improve clinician management of study drug.
5.5 Criteria for Temporarily Delaying Study Intervention	Condition added	Delay due to logistical reasons allowed to avoid unnecessary rescreening procedures
6.1 Study Intervention(s) Administered	Guidance added regarding appropriate dose when post-infusion FVIII levels are lower than expected	Reduce the potential for bleeds in participants with low titer anti-PEG antibodies.
6.8 Concomitant Therapy	Clarification added regarding emergency treatment at home during the first 2 weeks of study treatment	Appropriate emergency treatment of bleeds that must be managed at home without medical supervision.
8.2.3.1 Decreased Recovery	Section added	Specific treatment and laboratory evaluations added for participants with lower than expected recovery after the first exposures
8.3.8 Adverse Events of Special Interest (AESI)	Examples of Loss of Efficacy added	Clarification added to ensure safe management of study participants
	FVIII level and FVIII inhibitor testing guidance	Specific guidance only applies to study participants that have discontinued study

Section # and Name	Description of Change	Brief Rationale
	updated	drug.
10.2 Appendix 2: Clinical Laboratory Tests	Local laboratory testing guidance updated	Must be done as specified in the SoA, not just in cases where central laboratory results are not available.
10.6 Appendix 6: Protocol Amendment History	Section added	Documentation of changes made in prior amendments

Minor changes made throughout the document to correct typos, grammar, document headers, etc., are not individually summarized.

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1. Protocol Summary

1.1 Synopsis

Protocol Title:

A Phase 3, single-group treatment, open-label, study to evaluate the safety of BAY 94-9027 infusions for prophylaxis and treatment of bleeding in previously treated children aged 7 to <12 years with severe hemophilia A.

Short Title:

A Phase 3 safety study of BAY 94-9027 in children 7 to <12 years of age with severe hemophilia A

Rationale:
At the time of the initial biologic license application /marketing authorization application (BLA/MAA), the indication for BAY 94-9027 was restricted to previously treated hemophilia A patients 12 years and older, partly, because of the observation of an immune response to polyethylene glycol (PEG) in some children < 6 years, manifested as hypersensitivity and/or loss of efficacy (LoE). A significant decrease in the risk of an immune response to PEG was observed with an increase in age. Among the 25 previously treated patients, aged 7 to <12 years, in the pivotal study in pediatric patients <12 years of age with severe hemophilia A, no such cases were observed. However, due to the small sample size, as a safety margin, this age group (7 to <12 years) was excluded in the initial MAA. This study will address the potential risk of hypersensitivity and lack of drug effect associated with anti-PEG antibodies during the first 4 exposures to BAY 94-9027 in previously treated children 7 to <12 years of age with severe hemophilia A, and will provide supportive data for efficacy of prophylaxis treatment including long-term safety data.

Objectives, Endpoints, and/or Estimands:

Primary and secondary objectives and endpoints are described below. See Section 3 for the full list of objectives and endpoints.

Objectives	Endpoints
Primary objective (main study)	
Safety	
To assess safety and tolerability of BAY 94-9027 replacement therapy in previously treated patients 7- <12 years of age with severe hemophilia A	**Primary endpoint** • AESI (hypersensitivity and LoE*) associated with the first 4 EDs leading to discontinuation **Secondary endpoints** • Adverse drug reactions (ADRs) • Anti-drug antibody (ADA) development • Inhibitor development
Secondary objective (main study and extension study)	
To describe clinical efficacy of BAY 94-9027	**Secondary endpoints** • Annualized bleeding rate (ABR) • BAY 94-9027 consumption • Number of infusions/month and year (Annualized Infusion Rate)

AESI = adverse events of special interest, ED = exposure day
* As defined in Section 8.3.8.

Overall Design

Short Summary:

The purpose of this open-label, single-group, uncontrolled, prospective, multicenter study is to assess the safety of BAY 94-9027 in children aged 7 to <12 years with severe hemophilia A.

Study details:

- The treatment duration will be:
  - **Main study (Part A)**: 6 months and ≥ 50 exposure days (EDs)
  - **Extension study (Part B)**: 18 months

- The visit frequency will be twice a week for the first 4 EDs with study intervention, with visit frequency decreasing afterwards (see Section 1.3 SoA for details)

Number of Participants:

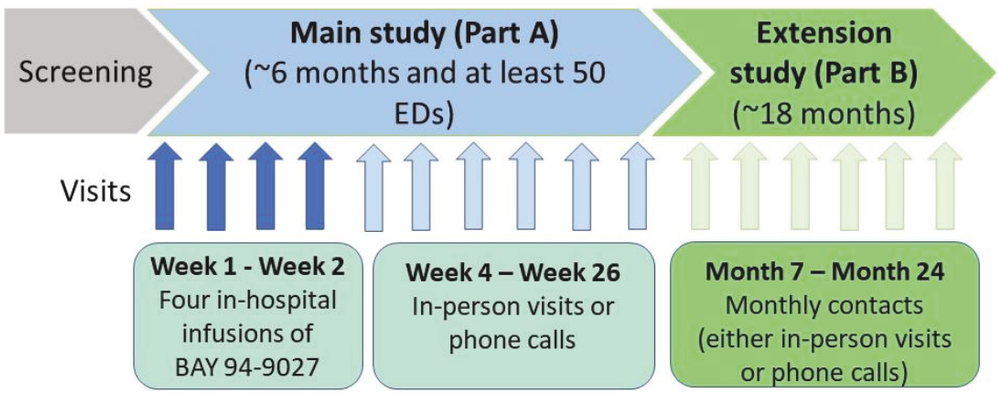
- At least 30 participants will be assigned to study intervention.
- Additional participants may be enrolled in the event of treatment discontinuation during the first 4 EDs of Part A for reasons other than adverse events of special interest (AESI).

Intervention Groups and Duration:

- **Part A**: Each participant will receive BAY 94-9027 intravenously (IV) as prophylactic treatment 2x/week, with a dose of 40 IU/kg (up to 60 IU/kg – at the investigator's discretion)
- **Part B**: Each participant may continue on prophylaxis dose regimen as prescribed in part A (40 – 60 IU/kg, 2x per week) or the prophylaxis regimen may be adjusted to 60 IU/kg IV every 5 days at the investigator's discretion

Data Monitoring/Other Committee: No

1.2 Schema



EDs = exposure days

1.3 Schedule of Activities (SoA)

Table 1–1: Schedule of Activities - main study (Part A)

Period	**SCR**	**Treatment**									
Visit number **Exposure day (ED)**	**V1**	**V2** **ED1**	**V3** **ED2**	**V4** **ED3**	**V5** **ED4**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11** **ED 50 /E.Disc.**
In person (IP) or phone call	**IP**	**IP**	**IP**	**IP**	**IP**	**IP or ☎[a]**	**IP**	**IP**	**☎**	**IP**	**IP**
Relative time **W = week, D=day**	**Up to - 30 Days**	**D1 (BSL)**	**W1**	**W2**	**W2**	**W4**	**W8**	**W12**	**W16**	**W20**	**W26 (Month 6)**
Allowed window		±1 days for all visits from V2 to V5, inclusive				±3 days for all visits from V6 to V11, inclusive					
Informed consent/assent	X										
Check inclusion/exclusion criteria	X	X									
Demography	X										
Physical examination (height and weight)	X							X			X
Neurological assessment		X [b]									X
Medical and surgical history	X										
Previous and concomitant medication	X	X	X	X	X	X	X	X	X	X	X
Vital signs		X [c]	X [c]	X [c]	X [c]						X
Haemo-QoL questionnaire [d]		X									X
Patient/Caregiver Global Impression of Severity		X									X
Patient/Caregiver Global Impression of Change											X
Laboratory assessments (chemistry and hematology) [e]	X	X [f]									X
PEG quantification		X [b]									X
Urine / serum biomarkers for renal function		X [b]									X
Immunogenicity (FVIII inhibitor, ADA) – pre-infusion [g,h]	X	X	X	X	X		X				X
FVIII levels [g] if no prior result available (Section 5.1)	X										
Recovery (pre and 15-30 min post-infusion FVIII levels) [g,h,i]		X	X	X	X						X

Table 1–1: Schedule of Activities - main study (Part A)

Period	**SCR**	**Treatment**									
Visit number **Exposure day (ED)**	**V1**	**V2** **ED1**	**V3** **ED2**	**V4** **ED3**	**V5** **ED4**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11** **ED 50 /E.Disc.**
In person (IP) or phone call	**IP**	**IP**	**IP**	**IP**	**IP**	**IP or ☎[a]**	**IP**	**IP**	**☎**	**IP**	**IP**
Relative time **W = week, D=day**	**Up to - 30 Days**	**D1 (BSL)**	**W1**	**W2**	**W2**	**W4**	**W8**	**W12**	**W16**	**W20**	**W26 (Month 6)**
Allowed window		±1 days for all visits from V2 to V5, inclusive				±3 days for all visits from V6 to V11, inclusive					
In-hospital infusion of BAY 94-9027		X	X	X	X						X [j]
AE review	X [k]	X	X	X	X	X	X	X	X	X	X
Dispense study intervention [l]					X		X	X	X	X	(X) [m]
Return used /unused study intervention							X	X		X	X
Diary review [n]			X	X	X	X	X	X	X	X	X

ADA = anti-drug antibodies (anti-PEG, anti-PEG IgM in all treated study participants; IgE only in study participants who experience a hypersensitivity reaction) ED = exposure days, BSL = baseline, E.Disc. = early discontinuation, FVIII = factor VIII, IP = in-person visit, QoL = Quality of Life, SCR = screening, V = visit,

a: At the investigator's discretion based on participant's condition.
b: May be performed at a visit other than baseline if the participant is already enrolled at the time Amendment 1 is implemented, PEG quantification and urine/serum biomarkers must be performed before infusion at the scheduled visit.
c: Vital signs to be taken before and after infusion.
d: QoL questionnaire: Haemo-QoL Kids Short Form (8-16 years old version).
e: See Section 10.2 for details on laboratory parameters.
f: Only chemistry collected at Visit 2
g: FVIII level and FVIII inhibitor tests must be done after a sufficient wash-out period depending on the participant's previous FVIII product – at least 48 hours or 72 hours for standard half-life (SHL) and extended half-life (EHL) FVIII products respectively (screening and baseline visits).
h: FVIII inhibitor tests and pre-infusion FVIII levels for recovery must be done after a wash-out period of at least 72 hours after previous dose of study intervention (V3, V4, V5, V7, and V11/E.Disc.). If a 72-hour wash-out period is not possible (e.g. participant received previous infusion within 48 hours), no restriction is needed during the first 4 EDs or at any visits for monitoring of ADA. In this scenario, recovery should also be measured without wash-out.
In case of early discontinuation, recovery is not required.
i: Local FVIII levels should be obtained to guide treatment for the next dose during the first 4 EDs.
j: In-hospital infusion will not be performed at early discontinuation visits for adverse events of special interest (hypersensitivity or loss of efficacy) or other reasons.
k: Only study procedure related AEs.
l: Unscheduled visits are permitted at any time at the discretion of the investigator. In addition, participants may visit the study center for study intervention and supplies.
m: Drug dispensing for extension study (Part B).
n: Dispense diary at V2.

Table 1–2: Schedule of Activities – extension study (Part B)

Extension visit number	**EV1–EV2**	**EV3**	**EV4–EV5**	**EV6**	**EV 7–EV 11**	**EV 12**	**EV 13–EV 17**	**EV 18 / E. Disc.**	**Follow-up[a]**
In person (IP) or phone call	☎	IP	☎	IP	☎	IP	☎	IP	☎
Month and allowed window	**Months 7-8[b]** ± 1week	**Month 9** ± 1week	**Months 10-11[b]** ± 1week	**Month 12** ± 1week	**Months 13-17[b]** ± 1week	**Month 18** ± 1week	**Months 19-23[b]** ± 1week	**Month 24** ± 1week	**7 to 14 days after EV18 / E. Disc.**
Physical examination (height and weight)		X		X		X		X	
Neurological assessment								X	
Concomitant medication	X	X	X	X	X	X	X	X	X
Vital signs				X		X		X	
Immunogenicity (FVIII inhibitor, ADA) [c]				X		X		X	
Recovery (pre and 15-30 min post-infusion FVIII levels) [c]				X		X		X	
In-hospital infusion of BAY 94-9027				X		X		X [d]	
AE review	X	X	X	X	X	X	X	X	X
Return used/ unused study intervention		X		X		X		X	
Dispense study intervention [e]	Intervention dispensed according to IxRS specification								
Diary review	X	X	X	X	X	X	X	X	
Haemo-QoL questionnaire [f]				X		X		X	
Patient/Caregiver questionnaires [g]				X		X		X	
Laboratory assessments (chemistry and hematology) [h]								X	
PEG quantification								X	
Urine/serum biomarkers for renal function								X	

ADA = anti-drug antibodies (anti-PEG, anti-PEG IgM in all treated study participants; IgE only in study participants who experience a hypersensitivity reaction), ED = exposure days, E.Disc. = early discontinuation, EV = extension visit, FVIII = factor VIII, IP = in-person visit

a: Follow-up call for early discontinuation in Part A and Part B.

b: One phone call per month for all months included in this window of time.

c: FVIII inhibitor tests and pre-infusion FVIII levels for recovery must be done after a wash-out period of at least 72 hours after previous dose of study intervention (EV6/E.Disc.).

Table 1–2: Schedule of Activities – extension study (Part B)

Extension visit number	**EV1–EV2**	**EV3**	**EV4–EV5**	**EV6**	**EV 7–EV 11**	**EV 12**	**EV 13–EV 17**	**EV 18 / E. Disc.**	**Follow-up[a]**
In person (IP) or phone call	☎	IP	☎	IP	☎	IP	☎	IP	☎
Month and allowed window	**Months 7-8[b]** ± 1week	**Month 9** ± 1week	**Months 10-11[b]** ± 1week	**Month 12** ± 1week	**Months 13-17[b]** ± 1week	**Month 18** ± 1week	**Months 19-23[b]** ± 1week	**Month 24** ± 1week	**7 to 14 days after EV18 / E. Disc.**

d: In-hospital infusion not performed at early discontinuation visits for adverse events of special interest (hypersensitivity or loss of efficacy) or other reasons.
e: Unscheduled visits are permitted at any time at the discretion of the investigator. In addition, participants may visit the study center for study intervention and supplies.
f: QoL questionnaire-: Haemo-QoL Kids Short Form (8-16 years old version).
g: Patient/Caregiver Global Impression of Severity and Patient/Caregiver Global Impression of Change.
h: See Section 10.2 for details on laboratory parameters.

2. Introduction

2.1 Study Rationale

At the time of the initial biologic license application /marketing authorization application (BLA/MAA), BAY 94-9027 has received marketing authorization for treatment and prophylaxis of bleeding in previously treated patients (PTPs) ≥ 12 years of age with hemophilia A.

The indication for BAY 94-9027 (Jivi) was restricted to previously treated hemophilia A patients 12 years and older, partly because of the observation of an immune response to PEG in some children < 6 years, manifested as hypersensitivity and/or loss of efficacy (LoE) (JIVI SmPC 2018, JIVI® Prescribing information 2018). The immune response associated with anti-PEG IgM antibodies was observed within the first 4 EDs in some children 2-5 years of age leading to study discontinuation in all cases. Clinical symptoms were mild to moderate acute hypersensitivity and/or LoE. All patients could revert back to their previous factor VIII treatment.

A significant decrease in the risk of an immune response to PEG was observed with an increase in age. Among the 25 PTPs, aged 7 to <12 years, in the pivotal study in pediatric patients < 12 years of age with severe hemophilia A, no such cases were observed. However, due to the small sample size, as a safety margin, this age group (7 to <12 years) was excluded in the initial BLA/MAA.

This study addresses the uncertainty of the risk of potential hypersensitivity and lack of drug effects associated with anti-PEG antibodies during the first 4 exposures to BAY 94-9027 in previously treated children with severe hemophilia A, 7 to <12 years of age. In addition, will provide supportive data for efficacy of prophylaxis treatment and long-term safety data.

2.2 Background

BAY 94-9027 is a recombinant FVIII (rFVIII) with extended half-life through reduced clearance from plasma by PEGylation while retaining the normal activity of the FVIII molecule. It has received marketing authorization for treatment and prophylaxis of bleeding (including perioperative management) in PTPs ≥ 12 years of age with hemophilia A (congenital FVIII deficiency) (JIVI SmPC 2018, JIVI® Prescribing information 2018).

Pharmacokinetics, clinical efficacy and safety of BAY 94-9027 for treatment of bleeds and prophylaxis in hemophilia A have been assessed in one Phase 1 study and two Phase 3 studies including previously treated severe hemophilia A patients 2 to 65 years of age (Coyle et al. 2014, Reding et al. 2017, Santagostino et al. 2020).

Pharmacokinetics, safety, and efficacy of BAY 94-9027 in pediatric patients <12 years of age were assessed in the PROTECT Kids study (study 15912; NCT01775618), a Phase 3 multicenter, open-label, noncontrolled study to assess BAY 94-9027 treatment for prophylaxis and treatment of bleeds in previously treated children (>50 ED) with severe hemophilia A. The study comprised a main study (in PTPs <12 years of age), Part 2 (in PTPs 2-5 years of age) and the extension study, and included a total of 73 patients, 44 in the age group < 6 years and 29 in the age group 6 to <12 years. The median total study duration was 5.4 years (N=73).

Efficacy of prophylaxis treatment and treatment of bleeds was demonstrated for both age groups (Santagostino et al. 2020). The geometric mean terminal half-life ($t_{½}$) for

BAY 94-9027 was 14.5 hours and 15.6 hours in patients aged <6 years (n = 14) and 6 to <12 years (n = 13), respectively (Shah et al. 2018).

No subjects developed inhibitory antibodies to FVIII (≥0.6 BU/mL) during the study. A clinical immune response associated with anti-PEG IgM antibodies, manifested as symptoms of acute hypersensitivity and/or LoE (AESI) was observed within the first 4 EDs in young children 2-5 years of age leading to study discontinuation in all cases (Santagostino et al. 2020). In cases of clinical immune response associated with anti-PEG IgM antibodies presenting with hypersensitivity reactions, these reactions were observed within 30 minutes of completion of study drug administration, and resolved within 30 minutes of occurrence without intervention. In all cases, clinical efficacy and recovery using the previous FVIII product was not impaired in the subjects affected. There was no immunoglobulin class switch to IgG, and the IgM titers disappeared over time suggesting no long-term memory response (Santagostino et al. 2020). No participant aged 7 to <12 years old (n = 25) experienced an AESI (hypersensitivity and/or LoE). A significant decrease in the risk of an immune response to PEG was observed with an increase in age. Thus, the clinical immune response associated with anti-PEG IgM antibodies, may be related to a developmental change in immunity, and although it is difficult to define a clear cut-off age for the change in risk, this phenomenon predominantly occurred in young children (2-5 years of age) with hemophilia A.

Immunogenicity to the PEG moiety in Jivi appears to be age related, as it is suggested by preliminary data from the initial patients dosed in this study. More specifically, this early data suggests that when an immune response occurs, it is less severe in this age group than that typically observed in younger children 2-5 years of age. This reduced immune response has been characterized by low titers of anti-PEG antibodies (1:1 to 1:4) with mild to moderate reductions in FVIII recovery during EDs 2-4. Continued dosing with Jivi has demonstrated decreased levels of anti-PEG antibodies and improved FVIII recovery. To better protect study participants against the potential for a bleed related to lower-than-expected FVIII levels, routine local FVIII recovery measurements should be performed at the clinical site for the first 4 EDs to evaluate the response to treatment in addition to performing FVIII recovery at the central lab. This standardized approach will enable the treating clinician to adjust the dose and dosing interval for the subsequent EDs.

2.3 Benefit/Risk Assessment

Relevant emerging safety data, e.g., serious adverse events (SAEs), suspected unexpected serious adverse reactions (SUSARs), and serious safety-related protocol deviations, will be communicated as soon as possible between the sponsor, all study sites and investigators and trial participants/parents/caregivers.

More detailed information about the known and expected benefits and risks and reasonably expected adverse events of BAY 94-9027 may be found in the Investigator's Brochure (IB).

2.3.1 Risk Assessment

Due to the substantial experience with pegylated FVIII replacement products, the risks are well established. The most relevant treatment related complication for class of FVIII replacement products, is the development of FVIII inhibitors. For previously untreated patients (PUPs), the risk to develop inhibitors is considered very common (approximately 30% to 50%) (Franchini et al. 2013, Peyvandi et al. 2016, Srivastava et al. 2020), whereas the risk for PTPs is considered uncommon (<1%). No confirmed case of inhibitor development was reported during the development program with BAY 94-9027 in PTPs.

Other known risks for class of FVIII replacement products are allergic type of hypersensitivity reactions which may progress to anaphylaxis including shock, cardiovascular events, and the possibility of catheter related complications. Data of more than 200 patients in the age range of 2 to 62 years demonstrated that these risks are not different for BAY 94-9027 administered to PTPs. No case of anaphylaxis was reported, and no serious cardiovascular event was observed.

A new risk identified during the development program for BAY 94-9027 is an immune response to PEG which resulted in LoE, observed as bruising or bleeding not responsive to treatment with BAY 94-9027 and very low recovery (sometimes undetectable) following infusion of BAY 94-9027 in the absence of FVIII inhibitors. LoE was accompanied by hypersensitivity reactions in some patients. This risk was most frequent in the age group less than 6 years and resulted in a premature termination of study treatment in approximately 23% (10/44) of cases in this age group. There were no cases of PEG immune response among the 25 patients, aged 7 to <12 years, and only 1/134 patients ≥12 years had a PEG-related hypersensitivity reaction leading to study discontinuation. During post-marketing surveillance (PMS) with >1,000 new patients starts, the incidence of clinical events likely associated with antibodies to the PEG moiety has been consistent with that observed in the clinical trials for patients ≥12 years of age. All events have occurred on EDs 2-4.

A potential class risk for pegylated FVIII replacement products is associated with PEG accumulation following long-term treatment. The dose of PEG contained with BAY 94-9027 is low relative to other pegylated products (e.g., certolizumab pegol) resulting in a low total weekly and monthly PEG exposure below the level of concern in the pediatric population of 0.4µmol-kg-month of PEG (EMA 2012). In distribution and excretion studies in rats, the 60 kDa PEG moiety of Jivi® was shown to be eliminated from organs and tissues, and excreted in urine and feces (Baumann et al. 2019).

In a long-term, 6-months chronic toxicity study in immunodeficient rats no indication of PEG accumulation or other effects related to administration of Jivi® were seen. ((JIVI SmPC 2018), Section 5.3).

In addition, no evidence for accumulation of PEG in plasma (median levels < 0.1 mg/L) nor in other organs such as kidneys, liver, and central nervous system was demonstrated for up to 7 years of continuous treatment in the clinical extension studies of Jivi® in children and adults (PTPs 2 - 62 years of age) (Mancuso et al. , Reding et al. 2021).

Blood samples will be collected at screening to confirm study eligibility, and during scheduled study visits as part of safety assessment for the study. The frequency of these assessments is likely more than is typical for standard of care. The study has kept the frequency of these assessments to the minimum required to reliably assess the safety of BAY 94-9027 in study participants. For the majority of participants in the study, the volumes drawn at any one visit are not expected to exceed more than 1% of total blood volume or 3% in any 1-month interval. Therefore, it is expected that the risk associated with blood draws is not more than would be expected with standard of care.

Table 2–1: Summary of Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Study Intervention		
Development of FVIII inhibitors	The formation of neutralizing antibodies (inhibitors) to FVIII is a known and listed AE for FVIII	Participants will be tested for FVIII inhibitors.

Table 2–1: Summary of Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	products. No confirmed case of FVIII inhibitor development was reported during the development program with BAY 94-9027	• Inhibitor titer is assessed at scheduled study visits. • Planned time points for all safety assessments are provided in the SoA (Section 1.3). The informed consent will outline the important identified and potential risks.
Anti-drug antibodies to PEG leading to hypersensitivity reaction and LoE	Hypersensitivity and LoE have been reported in previous clinical studies with BAY 94-9027, mainly in children <6 years, during the first 4 EDs. This was not observed in children in the age group 7-<12 years.	The first 4 doses of study intervention will be administered in the hospital under medical supervision, so that if a hypersensitivity reaction occurs, it can be adequately managed. Pre- and post-infusion FVIII levels will be measured intermittently as per SoA during the main study. Reporting these AEs as AESIs (Section 8.2.3.1 and Section 8.3.8) Inclusion of stopping rule for study intervention administration in study protocol (Section 10.1.8) The informed consent will outline the important identified and potential risks.
Hypersensitivity reaction in the absence of development of anti-PEG antibodies	Hypersensitivity reaction to exogenously administered FVIII is a known and listed AE for FVIII products and have occurred with BAY 94-9027. In completed clinical studies with BAY 94-9027, one 6-year-old patient developed hypersensitivity reaction in association with the first administration of BAY 94-9027	The first 4 doses of study intervention will be administered in the hospital under medical supervision, so that if a hypersensitivity reaction occurs, it can be adequately managed. The informed consent will outline the important identified and potential risks.
Study Procedures		
Pain and bleeding during blood draws	Blood draws are standard procedures for assessment of safety	Study procedures will be conducted at specialized hemophilia treatment centers by trained personnel.

2.3.2 Benefit Assessment

Hemophilia A is an X-linked, congenital, potentially life-threatening disease that is caused by a deficiency of FVIII and results in impaired blood clotting. Patients with hemophilia A require infusions of replacement FVIII to prevent and treat spontaneous and trauma-related bleeding episodes.

BAY 94-9027 is an extended half-life, recombinant FVIII (rFVIII) product approved for the prevention and treatment of bleeding episodes (including perioperative management) in PTPs ≥12 years of age with hemophilia A. Efficacy of BAY 94-9027 for treatment of bleeds and prophylaxis in hemophilia A was demonstrated in two Phase 3 studies including previously treated severe hemophilia A patients 2 to 65 years of age (Reding et al. 2017, Santagostino et al. 2020). The potential benefits of the study intervention to participants are less frequent dosing and less reliance on central venous catheters, which may reduce physical and

emotional burden for the child and his family, leading to better adherence. This, in turn, may translate into improved FVIII activity coverage and good prophylactic protection from bleeds.

2.3.3 Overall Benefit: Risk Conclusion

Taking into account the measures taken to minimize risk to participants in this study, the potential risks identified in association with BAY 94-9027 are justified by the anticipated benefits of prophylaxis treatment with BAY 94-9027 that may be afforded to study participants.

3. Objectives, Endpoints, and Estimands

Objectives	Endpoints
Primary objective (main study)	
Safety	
To assess safety and tolerability of BAY 94-9027 replacement therapy in previously treated patients 7- <12 years of age with severe hemophilia A	**Primary endpoint** • AESI (hypersensitivity and LoE*) associated with the first 4 EDs leading to discontinuation **Secondary endpoints** • Adverse drug reactions (ADRs) • Anti-drug antibody (ADA) development • Inhibitor development
Secondary objective (main study and extension study)	
To describe clinical efficacy of BAY 94-9027	**Secondary endpoints** • Annualized bleeding rate (ABR) • BAY 94-9027 consumption • Number of infusions/month and year (Annualized Infusion Rate)
Other	
To further investigate long-term safety	• Quantitative PEG measurement • Renal safety-related urine and serum biomarkers • Liver enzymes • Neurological assessment
To assess the impact of BAY 94-9027 in Health-related QoL	Patient-reported outcomes (PROs) questionnaires
To further investigate the study intervention and similar drugs (e.g., mode-of-action-related effects, safety) and to further investigate pathomechanisms deemed relevant to hemophilia and associated health problems	Various biomarkers (e.g., diagnostic, safety, pharmacodynamic, monitoring, or potentially predictive biomarkers)

AESI = adverse events of special interest, ED = exposure day
* As defined in Section 8.3.8.

Primary estimand

The primary clinical question of interest for the primary objective is:

What is the proportion of individuals with AESIs (hypersensitivity and LoE) associated with the first 4 EDs of BAY 94-9027 treatment and leading to discontinuation of BAY 94-9027 treatment in previously treated males, 7 to <12 years of age with severe hemophilia A, and

without inhibitors to FVIII, who do not discontinue study for other reason than an AESI before the fourth ED with or without emergency use of other FVIII medication?

The estimand is described by the following attributes:

Population	Previously treated (≥50 EDs) male individuals, 7 to <12 years of age, with severe hemophilia A (FVIII:C <1%) without inhibitors to FVIII (<0.6 BU/mL).
Endpoint	AESI (i.e., hypersensitivity or LoE, as defined in Section 8.3.8) associated with the first 4 EDs of BAY 94-9027 treatment leading to discontinuation.
Treatment condition	2x/week BAY 94-9027 prophylactic treatment at a dosage of 40 IU/kg, up to 60 IU/kg, with or without emergency use of other FVIII products (treatment policy strategy*).
Intercurrent events and strategies how to address them	• Individuals with the intercurrent event 'treatment discontinuation for any reason other than AESI before the fourth ED' will not be included in the assessment of the primary endpoint (principal stratum strategy*). • The intercurrent event 'emergency use of other FVIII products' is addressed by the treatment condition attribute following the treatment policy strategy* . Other relevant intercurrent events are not anticipated at this point in time.
Population level summary	Proportion of individuals who experience a primary endpoint AESI.

*: Treatment policy strategy, and principal stratum strategy refer to the strategies for addressing intercurrent events as described in the ICH E9 (R1) guideline

Rationale for estimand:

In the pivotal Phase 3 studies PROTECT VIII and PROTECT Kids, an immune response associated with anti-PEG IgM antibodies was observed primarily in children 2-5 years of age. The immune response manifested as symptoms of hypersensitivity and/or LoE. All events occurred during the first 4 EDs of BAY 94-9027 and all led to study discontinuation. The primary estimand has been chosen to estimate the unknown risk of such events in previously treated children, 7 to <12 years of age, with severe hemophilia A. Since these events might occur up to the fourth ED, event-free children discontinuing before the fourth ED is reached do not provide sufficient information and will be excluded from the population of interest. Use of other FVIII products is not expected but might happen in emergency cases. Exposure to another FVIII medication is not considered an ED in terms of the primary endpoint. Four EDs with BAY 94-9027 are needed for the assessment. All AESIs associated with the first 4 BAY 94-9027 treatments will be counted regardless of other FVIII exposure.

Secondary estimand

The key clinical question of interest for the secondary objective is:

What is the ABR of previously treated males 7 to <12 years of age with severe hemophilia A without inhibitors to FVIII, or neutralizing ADA, who are on a continuous prophylaxis treatment with BAY 94-9027 for at least 3 months up to time when at least 50 EDs are reached (approximately 6 months) and for further 6 months by and across treatment regimens without major surgery and regardless of emergency use of other FVIII medication?

The estimand is described by the following attributes:

Population	Previously treated (≥50 EDs) male individuals, 7 to <12 years of age, with severe hemophilia A (FVIII:C <1%) without inhibitors to FVIII (<0.6 BU/mL).
Endpoint	Number of bleeds per individual observation period of continuous prophylactic treatment (overall and per treatment regimen) of at least 3 months up to time when at least 50 EDs are reached (approximately 6 months) and for further 18 months of BAY 94-9027 treatment. [In this study, the 6- and 2- year periods are reflected by Part A and Part B of the study.]
Treatment condition	2x/week prophylactic treatment with BAY 94-9027 at a dosage of 40 IU/kg, up to 60 IU/kg, with option to change to every 5 days prophylactic treatment with BAY 94-9027 at a dosage of 60 IU/kg IV, after at least 50 EDs (with start of Part B) with or without emergency use of other FVIII medication (treatment policy strategy*).
Intercurrent events and strategies how to address them	• The intercurrent events 'treatment discontinuation for any reason before Month 3' and 'development of an inhibitory antibody to FVIII or ADA that neutralizes activity sufficiently to interfere with effective treatment' will be addressed by the endpoint attribute following the principal stratum strategy*. • The intercurrent events 'treatment discontinuation for any reason after Month 3' and 'emergency use of other FVIII medication' will be addressed by the treatment policy strategy*. • The intercurrent event 'emergency major surgery' is addressed by the endpoint attribute following the hypothetical strategy*. The time of the surgery will not be considered for the observation period and bleeds during the time of the surgery (i.e., bleeds related to the surgery procedure) will not be counted. An individual with this intercurrent event will be analyzed as if the surgery had not happened. Other relevant intercurrent events are not anticipated at this point in time.
Population level summary	Mean and 95% confidence interval for ABR estimated by a Negative Binomial regression.

*: Treatment policy strategy, principal stratum strategy, and hypothetical strategy refer to the strategies for addressing intercurrent events as described in the ICH E9 (R1) guideline

Rationale for estimand:

Efficacy is assessed by the number of bleeds per year. The ABR during continuous prophylaxis treatment with BAY 94-9027 is of clinical interest in this study. An observation period shorter than 3 months does not constitute a stable prophylaxis treatment and does not allow a reliable evaluation of annualized bleeding rates. Individuals who develop a FVIII inhibitor or an ADA that neutralizes activity of BAY 94-9027 sufficiently to interfere with effective treatment require other treatment modalities and are therefore excluded from the population of interest. An emergency major surgery is a short-term event that requires specific treatment and leads to surgery-specific bleeding episodes. While the surgery period does not contribute to the ABR of prophylaxis treatment, the non-surgery related bleeds and treatment period can and will be evaluated. Bleeds treated with another FVIII product in an emergency case will be counted for the ABR as they occurred during prophylaxis treatment with BAY 94-9027.

4. Study Design

4.1 Overall Design

This is an open-label, single-group, uncontrolled, prospective, multicenter study.

It comprises of the main study (Part A) and the extension study (Part B).

Part A will last for 6 months and at least 50 EDs. Extension study (Part B) will last 18 months.

For detailed visit schedule, refer to Section 1.3. Treatment administration is described in Section 6.

4.2 Scientific Rationale for Study Design

The study design is similar to that of the previous study with the study intervention in pediatric patients (PROTECT Kids study) in order to allow for pooling of data. Although, the safety events under evaluation had only been observed in the young age group < 6 years in the previous study, this study will closely monitor safety during the first 4 ED by laboratory and clinical parameters in order to assess the occurrence of the AESI in the age group 7 to <12 years. The additional 30 participants will provide a pooled sample size of 55 participants in the proposed age group.

4.3 Justification for Dose

40 IU/kg IV was the mean prophylaxis dose and 60 IU/kg IV was the upper dose range during the PROTECT Kids study. During the extension study, participants may also be treated with 60 IU/kg IV every 5 days which was also an effective dose used in the PROTECT Kids study.

4.4 End of Study Definition

The end of the study is defined as the date of the last visit of the last participant in the study globally.

A participant is considered to have completed the study if he has completed all periods of the study including the last visit.

Primary completion date is the date when the last participant completes Month 6 visit (or discontinues early).

5. Study Population

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

5.1 Inclusion Criteria

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

Age

1. Participant must be 7 to <12 years of age at the time of parent / legal guardian signing the informed consent

Type of participant and disease characteristics

2. Participants with known medical history of severe hemophilia A (participant's own FVIII activity [FVIII:C] <1%. FVIII:C) based on reliable prior documentation in clinical records of the participants. If no reliable documentation is available, FVIII activity must be measured at the time of screening after a 48-72 hours wash-out period (depending on his previous product).

Sex

3. Male

Treatment

4. Participants must be previously treated with FVIII concentrate(s) (plasma derived or recombinant) for a minimum of 50 EDs at the time of signing the informed consent.

Informed consent and Assent

5. Participant has understood the study and if appropriate for his age, has signed an informed assent. The parent(s) or guardian(s) is capable of giving signed informed consent as described in Section 10.1.3 which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol.
6. Willingness and ability of participants and/or parents /caregivers to complete training in the use of the electronic patient diary (EPD) and to document infusions during the study.

5.2 Exclusion Criteria

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

Medical conditions

1. History of FVIII inhibitors. Inhibitor to FVIII is defined as a titer ≥0.6 BU/mL (Nijmegen-modified Bethesda assay) or clinical history suggestive of inhibitor requiring modification of treatment. Participants with a maximum historical titer of ≤1.0 BU/mL on no more than 1 occasion with the classical Bethesda assay but at least 3 subsequent negative results [<0.6 BU/mL] are eligible.
2. Current evidence of inhibitor to FVIII measured using the Nijmegen-modified Bethesda assay (≥0.6 BU/mL) at the time of screening (central laboratory). Participants should not receive FVIII within at least 48 hours prior to the collection of

screening samples (See Section 1.3) and should have FVIII administered within the prior 2-3 weeks

3. Any other inherited or acquired bleeding disorder in addition to hemophilia A (e.g., von Willebrand disease, hemophilia B)
4. Platelet count <100,000 cells/µL
5. Serum creatinine > 2x upper limit of normal
6. Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) > 5x upper limit of normal
7. Known hypersensitivity or allergic reaction to drug substance, excipients or mouse or hamster protein
8. Any other significant medical condition that the investigator feels would be a risk to the participant or would impede the study

Prior/concomitant therapy

9. Requires any pre-medication to tolerate FVIII treatment (e.g., antihistamines)
10. Planned major surgery during the study
11. Any individual who is currently receiving or received chemotherapy, immune modulatory drugs, or has /had chronic use of oral or intravenous (IV) corticosteroids (> 14 days) within the last 3 months, other than anti-viral therapy
12. Any individual who received commercially available subcutaneous factor substitution therapy (emicizumab) within the last 6 months

Prior/concurrent clinical study experience

13. 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 study entry or previous participation in a clinical study with BAY 94-9027.

Other exclusions

14. Close affiliation with the investigational site; e.g., a close relative of the investigator, dependent person
15. Otherwise vulnerable participants other than being a child
16. The participant is identified by the investigator as being unable or unwilling to perform study procedures

5.3 Lifestyle Considerations

Not applicable.

5.4 Screen Failures

A screen failure occurs when a participant or his legal guardian consents 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, and eligibility criteria.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened once. Rescreened participants should be assigned a new participant number.

5.5 Criteria for Temporarily Delaying Study Intervention

The following conditions may allow a participant to start the study intervention once the conditions have resolved and the participant is otherwise eligible:

- Current febrile illness (temperature 38.0ºC [100.4º F]) or other acute illness within 48 hours before the first study intervention administration at baseline visit. If such an intercurrent acute event occurs, the screening period can be prolonged by 2 weeks without a need to repeat the screening assessment.
- Occurrence of a bleed within the required wash-out period for the baseline visit. If such an intercurrent acute event occurs, the screening period can be prolonged by 2 weeks without a need to repeat the screening assessment. This is only allowed once.
- Participant is otherwise eligible and his condition is medically stable, but the baseline visit did not occur for logistical reasons (eg, study intervention not available at site). In this instance, the screening period may be prolonged by additional 4 weeks without a need to repeat the screening assessment. This is only allowed once.

6. Study Intervention(s) and Concomitant Therapy

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

Table 6–1: Study Intervention(s) Administered

Intervention Name	Damoctocog alfa pegol
Dosage (For Prophylaxis)	**Main study (Part A)**: 40 IU/kg (up to 60 IU/kg at the investigator's discretion), 2 times per week (2x/week) with the first 4 infusions under medical supervision. Thereafter, participants will continue their treatment as home treatment. Dose may be increased up to 60 IU/kg (rounded up to full vials) if needed at any time during the study at the investigator's discretion. Potential reasons for a higher dose are e.g., presence of target joints, known short half-life of previous FVIII, high physical activity level, individual need for high trough FVIII levels. Post-infusion FVIII levels may be lower than expected after the first exposures (e.g., recovery of <1.2 kg/dL) and may be related to low titer anti-PEG antibodies. CCI [redacted]

Table 6–1: Study Intervention(s) Administered

	Extension study (Part B): Each participant may continue on prophylaxis dose regimen as prescribed in part A (40 – 60 IU/kg, 2x per week) or adjustments to prophylaxis dose / dose frequency can be made at the investigator's discretion (based on the bleeding events and individual needs): - Dose may be increased to 60 IU/kg (rounded to full vials) - Dose frequency may be decreased to every 5 days (prophylaxis dose: 60 IU/kg rounded to full vials) Prescribed doses for prophylaxis infusions higher than approximately 60 IU/kg (including rounding to full vials) have not been studied and therefore are not recommended. Rounding to full vials could result in up to 75 IU/kg for some low body weights. This is acceptable in children. The dose/kg decreases with increase in weight. All treatment decisions for identifying the appropriate prophylactic treatment regimen should be guided by clinical judgment based on individual participant's characteristics and treatment response. Bleeds will be treated with BAY 94-9027 as per the investigator's instruction. The appropriate treatment of bleeding events is left to the discretion of the treating physician, local clinical practice, and may be extrapolated from published guidelines (e.g., World Federation of Hemophilia [WFH], International Society on Thrombosis and Haemostasis [ISTH], World Health Organization [WHO]). The dose for prophylaxis and bleeding will be rounded up to the available vial size. If rounding up is not acceptable, rounding down is possible according to investigator discretion.
Type	Biologic
Route of Administration	Intravenous (IV) infusion delivered over 1 to 15 minutes, according to total volume. It is recommended to use a peripheral venous access. If a participant has a central venous access device (CVAD), the use of this device is allowed, but a peripheral access should be evaluated and is preferred for the study intervention. Participants or caregivers should only self-infuse if they have been trained by the healthcare provider or hemophilia center. Participants may only self-infuse under supervision of their caregiver.
Use	Experimental
Unit Dose Strength	500 IU/vial, 1000 IU/vial
Packaging and Labeling	**Packaging and Labeling:** Study intervention will be provided as lyophilized powder in a glass vial. Each glass vial will be provided with a prefilled syringe of the appropriate amount of sterile ''water for injection', European Pharmacopoeia and US Pharmacopeia, for reconstitution. Each glass vial will be labeled as required per country requirement.
[Current/Former Name(s) or Alias(es)]	Commercial name: Jivi® / BAY 94-9027

For each of the prophylaxis regimens, participants should adhere as closely as possible to the assigned dosing frequency. The day of treatment may vary within ±1 day to accommodate life events. Occasional extra infusions prior to activities or events that would be expected to result in an increased risk of bleeding are permitted, but should not result in a change in the assigned dosing schedule.

In case of severe, potentially life-threatening bleeding events, or the need for unplanned or emergency surgery, or if the investigational product cannot be obtained in a timely manner, the participant should be managed following local standard of care, using readily available factor products.

6.1.1 Medical Devices

The BAY 94-9027 vials will be supplied with the necessary medical devices to facilitate the preparation and infusion of the study intervention. The medical devices that are used in this study are the same as those marketed with Jivi, as well as Kovaltry, a rFVIII product manufactured by the Study Sponsor and is indicated for use in patients with congenital hemophilia A including patients in age group < 12 years of age.

The medical devices provided by the sponsor for use in the study are:

- Vial adapter
- Prefilled syringe containing sterile Water for Injection
- Administration set

In case device deficiencies occur (including malfunction, use error and inadequate labeling) this shall be documented and reported by the investigator to the sponsor throughout the clinical investigation (see Section 8.3.10) and appropriately managed by the sponsor.

6.2 Preparation, Handling, Storage, and Accountability

Instructions for the preparation of the study intervention according to the current approved Jivi® prescribing information will be provided to the participants.

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 eligible participants may receive study intervention and only authorized site staff may 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.

In accordance with the approved BAY 94-9027 labeling, BAY 94-9027 must be stored under refrigeration (+2°C to +8°C) at the site until dispensing. Freezing must be avoided.

At participants' homes, BAY 94-9027 must be stored under refrigeration (+2°C to +8°C) or may be stored for a single period of up to 6 months at temperatures up to +25°C or 77°F. Freezing must be avoided.

Reconstituted concentrate should be infused promptly (within 3 hours of reconstitution). Parents/caregivers will be provided with detailed instructions for proper storage of the study intervention at home.

6.3 Measures to Minimize Bias: Randomization and Blinding

Not applicable.

6.4 Study Intervention Compliance

When participants are dosed at the site, they will receive study intervention directly from the investigator or designee, under medical supervision. The date and time of each dose administered in the clinic will be recorded in the source documents and electronic case report forms (eCRFs).

When participants are dosed at home, the information will be recorded in EPD (see Section 8.1). Data on infusions for prophylaxis and treatment of bleeds will be collected. The parent/caregiver will interact with the investigator or delegate to verify and complete the EPD entries.

Data on the EPD will be transmitted after each treatment or bleeding event is entered. The EPD data will be used to assess compliance with the prophylaxis treatment schedule and with the recording of all treatments and bleeding events, and to support the documentation of the study intervention inventory.

Participation in the study may be terminated at the sponsor's discretion if a participant fails to comply with the above protocol requirements.

All used and unused vials of study intervention must be returned to the study center at each study visit. At the end of the study, all used and unused study intervention vials will be counted by the sponsor’s representative for final drug accountability.

6.5 Dose Modification

See Table 6–1 (Section 6.1) for potential dose modifications.

6.6 Continued Access to Study Intervention After the End of the Study

After the end of the study, the participants will not have access to the study intervention. Subsequent treatment will be mutually agreed upon by the parents/caregivers and the investigator.

6.7 Treatment of Overdose

No symptoms of overdose have been reported during the clinical development program for BAY 94-9027. If overdose occurs, contact the sponsor immediately. Decisions regarding dose interruptions or modifications will be made by the investigator in consultation with the Medical Monitor based on the clinical evaluation of the participant. The participant has to be closely monitored for any AE/SAE and laboratory abnormalities.

6.8 Concomitant Therapy

Any medication (including over-the-counter or prescription medicines, recreational drugs, vitamins, and/or herbal supplements) or other specific categories of interest that the participant received within 3 months of study enrollment, is receiving at the time of study 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

History of vaccinations received within 2 years of study enrollment (including vaccinations for COVID-19) should be collected for all participants.

Prior use of pegylated medications (e.g., PEG- interferon, PEG-anti-tumor necrosis factor [TNF], PEG-vaccine) will be collected for all participants.

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

Bleeds which occur during the screening period through ED 4 will be treated with the participant's own FVIII product. Thereafter, BAY 94-9027 will be used as the sole FVIII source for on-demand treatment of bleeds. In situations with a very low local recovery (see Section 8.2.3.1 for decreased recovery definition) after ED 1 through ED 4, study participants may administer their previous FVIII drug at home.

Pre-medications to tolerate treatment with BAY 94-9027 are not allowed. The use of topical anesthetics prior to venipuncture is permitted.

No other experimental drugs may be taken during the participation in this study.

No immunosuppressive/immunomodulatory drugs may be taken during the study. If such therapy is deemed necessary for the participant's welfare, or due to pre-existing illness, the situation should be discussed with the sponsor before enrollment. Medications which cause a bleeding diathesis (for example, acetylsalicylic acid) are contraindicated in any individual with hemophilia and should be avoided, except as specifically prescribed by a treating physician. Use of non-steroidal anti-inflammatory drugs, cyclooxygenase-2 (COX-2) inhibitors, or brief courses of corticosteroids to treat pain or acute synovitis, or inhaled or topical steroid medications (as for the treatment of asthma or eczema) are allowed if specifically prescribed by a treating physician.

6.8.1 Rescue Medicine

In the event of an AESI leading to discontinuation of study intervention, the participant will switch back to his previous FVIII medication.

7. Discontinuation of Study Intervention and Participant Discontinuation/Withdrawal

7.1 Discontinuation of Study Intervention

In rare instances, it may be necessary for a participant to permanently discontinue study intervention. If study intervention is permanently discontinued, the participant will not remain in the study. See the SoA (Section 1.3) for data to be collected at the time of discontinuation of study intervention and follow up and for any further evaluations that need to be completed.

Additional participants may be enrolled in the event of treatment discontinuation during the first 4 EDs of Part A for reasons other than AESI.

A participant will be withdrawn from the study and/or study intervention in the following cases:

- A positive inhibitor result at Baseline visit (Visit 2)
- At the request of the sponsor

- If, in the judgment of the investigator or the sponsor, the participant is not compliant with the protocol
- Development of an inhibitory ADA that neutralizes BAY 94-9027 activity sufficiently to interfere with effective treatment or requires use of another FVIII product to treat bleeds
- Development of an inhibitory antibody to FVIII that neutralizes activity sufficiently to interfere with effective treatment or requires use of a bypassing agent to treat bleeds
- Lack of response to treatment (other than due to an inhibitor)
- Anaphylaxis or severe hypersensitivity reaction (CTCAE version 5.0, Grade 3 or greater) associated with use of BAY 94-9027. See Section 10.1.8, study stopping rules, for more details
- Failure to comply with scheduled appointments for study-related testing or with EPD data entry to an extent that compromises collection of critical data

Use of another FVIII product for the treatment of bleeding (e.g., in an emergency) will not result in mandatory withdrawal of the participant.

Prolonged periods >14 days or repeated breaks in the prophylaxis schedule should be avoided and could result in the study participant being removed from the study.

7.2 Participant Discontinuation/Withdrawal from the Study

The legal guardian and the pediatric participant have the right to withdraw permission (consent or assent, respectively) at any time during the study. If the study staff identify any reluctance in the legal guardian or pediatric participant (e.g., signs of verbal or physical dissent) about continued participation in the study, the pediatric participant's continuation in the study should be reevaluated. The same principles that govern permission/assent/consent also govern its withdrawal.

A participant will be withdrawn from the study for any of the following reasons:

- Withdrawal of consent or assent if applicable (A pediatric participant's dissent should be respected.)

At the time of discontinuing from the study, if possible, an early discontinuation visit should be conducted, as shown in the SoA. See SoA (Section 1.3) 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 from the study intervention and the study at that time.

If the participant/parent/legal guardian withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.

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, counsel the participant on the importance of maintaining the assigned visit schedule, and ascertain whether 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, by telephone calls, and if necessary, a certified 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/she will be considered to have withdrawn from the study.

8. Study Assessments and Procedures

- Study procedures and their timing are summarized in the SoA (Section 1.3). 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 (Section 1.3), is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- 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 timeframe defined in the SoA.

8.1 Efficacy Assessments

Planned timepoints for all efficacy assessments are provided in the SoA (Section 1.3).

Efficacy endpoints (bleeding episodes and BAY 94-9027 consumption) will be collected in the EPD. Parents/caregivers or participants, if intellectual status allows, will be provided with EPDs for the entire study and will be trained in the use of the device. Investigators or their delegate will interact with parents/caregivers or participants on a regularly scheduled basis to verify the data on the EPD for accuracy and completion. Thus, the EPD will be considered the primary source for these data.

8.1.1 BAY 94-9027 consumption

Information on study intervention administration must be captured in either the eCRFs or in the EPDs, but not both. Information should not be duplicated.

The following guidance should be used for clarification of whether the information should be recorded in the EPDs or in the eCRFs:

- All use of study intervention outside the hospital/clinic should be recorded in the EPD.
- Use of study intervention in the hospital/clinic as defined in the protocol (e.g., at protocol-defined visits for FVIII recovery) or during an emergency major surgery should be recorded in the eCRFs.
    - In the extremely unlikely event that an infusion at a protocol-defined visit is given for a bleed, the information should be recorded in the EPD rather than the eCRFs, since additional information needs to be collected for bleeding that is not collected in eCRFs.
    - Regular prophylaxis infusions that are not defined in the protocol as being administered in the hospital/clinic at a specific visit should be recorded in the EPD regardless of whether they are administered in the hospital/clinic (e.g., infusion information for a participant whose infusion would have been given at home but had to be given in the hospital because of venous access should be recorded in the EPD).

Information recorded in the EPD will include:

- Date and time
- Vial numbers / number of vials and units administered
- Reason for treatment
    - Prophylaxis
    - Spontaneous bleed first treatment
    - Trauma bleed first treatment
    - Minor surgery
    - Follow-up treatment
    - Unscheduled/preventative prophylaxis (for physical activities, suspected or non-evident bleeding following identified trauma)

8.1.2 Recording of Bleeding Episodes

All bleeding episodes occurring after first dose of study intervention (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:

- Date and time of onset
- Type of bleeding (spontaneous, trauma, joint, muscle, skin/mucosal, internal, other)
- Location
- Intensity (mild, moderate, severe)

- Treated (yes/no):
  - If “yes”: Date and time
  - Product used: Study intervention / other drug
  - Doses

If BAY 94-9027 is used for the treatment of a bleeding episode, the response to treatment (excellent, good, moderate, poor, or none).

For guidance to the participants’ parents/caregivers, the following definitions for response to treatment are suggested. Individual responses may vary:

- **Excellent**: Abrupt pain relief and /or improvement in signs of bleeding with no additional infusion administered
- **Good**: Definite pain relief and/or improvement in signs of bleeding, but possibly requiring more than one infusion for complete resolution
- **Moderate**: Probable or slight improvement in signs of bleeding, with at least one additional infusion for complete resolution
- **Poor (or None)**: No improvement or condition worsens.

8.1.3 Clinical Outcome Assessments

8.1.3.1 Hemophilia Specific Quality of Life (Haemo-QoL) Questionnaire

In this study, the Haemo-QoL Short Form Questionnaire for children 8-16 years old will be used by all participants including participants who are 7- <8 years of age.

The Haemo-QoL Short Form contains 35 questions covering 9 domains: Physical Health, View of Yourself, Family, Friends, Others, Sports, Dealing, and Treatment.

The respondent burden for this questionnaire is approximately 15 minutes. The participant/parent/legal guardian will complete the questionnaire and the data will be entered in eCRF by the investigator or study site staff.

8.1.3.2 Patient/Caregiver Global Impression of Severity and Change

These 4 instruments are made of one single-item measure. They will explore patient--perceived and caregiver-perceived overall severity and change in health status since the start of study intervention. These instruments will be used to anchor the scores of Haemo-QoL. The participant/parent/legal guardian will complete the questionnaire and the data will be entered in eCRF by the investigator or study site staff.

The respondent burden for both questionnaires is approximately 2 minutes.

8.2 Safety Assessments

The safety assessments for the study include:

- (S)AEs, including AESI, AEs leading to discontinuation of study intervention (Section 8.2.3.1)
- FVIII inhibitor development using the Nijmegen-modified Bethesda assay. The first positive inhibitor test after a participant has started treatment with study drug will be

confirmed by testing a second (separately drawn) sample in a central laboratory. (Section 8.3.9)

- Anti-drug antibodies
- Physical examination findings, vital signs and laboratory values (Section 8.2.1 to 8.2.3)
- Evaluation of concomitant medication (Section 6.8)
- Long-term safety assessments:
  - Quantitative PEG measurement
  - Liver enzymes
  - Urine and serum biomarkers
  - Neurological assessment.

Planned time points for all safety assessments are provided in the SoA (Section 1.3). Clinically significant abnormal findings will be reported as AEs in the eCRF

8.2.1 Physical Examinations

A complete physical examination will include a review of body systems, and measurement of body height (cm), and weight (kg).

Standard neurological assessment will be performed by the investigator (neurologist not required) at the timepoints indicated in the SoA (Section 1.3).

8.2.2 Vital Signs

Measurement of vital signs will include: systolic and diastolic blood pressure, heart rate, and body temperature. Vital signs will be measured before and after administration of study intervention at time points indicated in the SoA (Section 1.3).

8.2.3 Clinical Safety Laboratory Tests

- See Section 10.2 for the list of clinical laboratory tests to be performed and the SoA (Section 1.3) for the timing and frequency.
- The investigator must review the laboratory report, document this review, and record any clinically significant changes occurring during the study as an AE. The laboratory reports must be filed with the source documents.
- Abnormal laboratory findings associated with the underlying disease are not considered clinically significant 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 or within 1 week after the last dose of study intervention should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the investigator or the Medical Monitor.
  - If clinically significant 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 tests, 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 tests 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.

8.2.3.1 Decreased recovery

In the event that recovery is lower than expected based on local FVIII post-infusion levels after the first infusions (e.g., recovery of <1.2 kg/dL):

- Increase dose to 60 IU/kg, and/or
- Additional prophylaxis infusion may be added
- Assess response to treatment with local assessment of recoveries, post-infusion levels

In patients with positive anti-PEG ADAs, obtain the following weekly until antibody titers are declining and FVIII recovery is stable.

- One each for both local and central lab:
  - Pre-infusion FVIII blood/plasma samples
  - FVIII blood/plasma samples 15-30 min post infusion for recovery
- One for central lab:
  - Blood/plasma sample for anti-PEG IgM

Once antibody titers are declining and FVIII recovery is stable, assess FVIII recovery and ADA monthly until ADAs disappear.

For study participants that have discontinued study drug, FVIII inhibitor tests must be done after a sufficient wash-out period depending on the FVIII product the participant is receiving – at least 48 hours or 72 hours for SHL and EHL FVIII products respectively

8.3 Adverse Events (AEs), Serious Adverse Events (SAEs) and Other Safety Reporting

The definitions of adverse events (AEs) and SAEs can be found in Section 10.3.

AEs will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legal guardian).

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following up all AEs including AEs that are serious, considered related to the study intervention or study procedures, or that caused the participant to discontinue the study intervention (see Section 7).

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

8.3.1 Time Period and Frequency for Collecting AE and SAE Information

(S)AEs (including AESI) will be collected from the start of study intervention until the last visit at the timepoints specified in the SoA (Section 1.3). (S)AEs which are related to protocol-required study procedures, e.g., (S)AE related to invasive study procedures will be recorded as (S)AEs from the signing of the ICF.

Any medical occurrences/conditions that begin in the period between signing ICF and the start of study intervention, and which are not related to a protocol-required study procedure, will be recorded as medical history/current medical conditions, not as AEs.

All SAEs and AESIs will be recorded and reported to the sponsor or designee immediately and under no circumstance should this exceed 24 hours of learning of the event, 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 information on AEs or SAEs 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/she 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

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

Clinical Presentation of Adverse Events

Study site staff should instruct the legal guardians and caregivers on how to report signs and symptoms (e.g., crying and pain) in the individual pediatric participant. They will be instructed to report both specific and non-specific symptoms (including vomiting, diarrhea, sleepiness, variation in the intensity, etc.). These non-specific symptoms may be the only manifestations of some adverse reactions observed in children. Care should be taken that the clinical presentation of adverse reactions is not misinterpreted as the manifestation of a pre-existing or unrelated condition.

Moreover, symptoms that are dependent on participant communication ability (e.g., nausea, pain, mood alterations) in younger or mentally disabled children could potentially be at risk for under- or mis-reporting.

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 AESI (as defined in Section 8.3.8), 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 provided in Section 10.3.

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 toward 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 (IRBs)/independent ethics committees (IECs), and investigators.
- 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 IB and will notify the IRB/IEC, if appropriate according to local requirements.
- For all studies except those using medical devices, investigator safety reports must be prepared for SUSARs according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.

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

The following disease-related events (DREs) are common in patients with hemophilia A and can be serious/life-threatening:

- Bleeding event

Any bleeding event 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: If the bleeding fulfills the criterion for an SAE (e.g., results in hospitalization), then the event should be recorded and reported as an SAE (Section 10.3.4).

NOTE: If either of the following conditions applies, then the event must be recorded and reported as an SAE (instead of a DRE):

- The event is, in the investigator's opinion, of greater intensity, frequency, or duration than expected for the individual participant

  OR

- The investigator considers that there is a reasonable possibility that the event was related to study intervention.

8.3.5 Pregnancy

Not applicable in this pediatric male participant population.

8.3.6 Cardiovascular and Death Events

Death will be reported with the known cause of death as a SAE.

8.3.7 Disease-related Events and/or Disease-related Outcomes Not Qualifying as AEs or SAEs

See Section 8.3.4 for DREs bleeding.

8.3.8 Adverse Events of Special Interest (AESI)

The AESI in this study are:

Hypersensitivity: defined as an immune reaction related to the administration of study intervention (BAY 94-9027). Hypersensitivity reactions may also occur in the absence of anti-PEG antibodies. It does not include hypersensitivity reactions which are not related to drug administration such as but not limited to rash related to contact dermatitis.

The first 4 infusions of study intervention will be administered under medical supervision. Participants will be monitored at the site for at least 60 minutes after infusion of study intervention. If allergic or anaphylactic reactions occur, the infusion will be stopped immediately and symptomatic treatment and therapy for hypersensitivity should be instituted, as appropriate. Participants will be made aware that the potential occurrence of chest tightness, dizziness, mild hypotension, and nausea during or after the infusion can constitute an early warning for hypersensitivity and anaphylactic reactions. In such cases, the participant should immediately notify the investigator or the site staff of these symptoms.

- LoE, associated with anti-PEG antibodies, has been observed primarily in previously treated hemophilia A patients 2-5 years of age within the 4 EDs to BAY 94-9027. LoE can present as bleeding, and must be confirmed by low recovery or post-infusion FVIII level, and a negative FVIII inhibitor test. When LoE is suspected, a sample for anti-PEG antibodies should be sent to the central lab.

  The following **are** considered LoE, even in the absence of a bleeding event:

  - Post-infusion FVIII that is not detectable or less than 15% with high titer (1:16 or greater) PEG IgM antibodies
  - Recovery is insufficient due to anti-PEG IgM antibodies to maintain FVIII concentrations via modification of the dose and/or dosing interval to maintain adequate prophylaxis against bleeding

  A reduced recovery/post-infusion FVIII level **is not** considered LoE if adequate prophylaxis can be achieved with an increased dose and/or decreased interval (generally, recovery >0.5 kg/dL).

The following information needs to be included on the eCRFs: time point of AESI in relation to administered study intervention, cumulative number of infusions of study intervention received as of time of adverse event, causal relation, duration, severity, symptoms, concomitant symptoms/disease, treatment, vaccination and time point, outcome, and history of previous allergic reactions.

8.3.8.1 Clinical guidance for hypersensitivity reactions requiring treatment

A: In the event of a hypersensitivity reaction occurring at the study site, while study participant is under medical supervision, the following is to be done:

1. Prompt treatment of the hypersensitivity reaction as per local standard of care/guidelines
2. Further observation for 1 hour after resolution of symptoms
3. Obtain
    a. Two blood/plasma samples each for FVIII level, and FVIII inhibitor (1 for local lab and one for central lab. Note: sample for FVIII inhibitor can be omitted if already collected prior to infusion of study intervention as per SoA (Section 1.3 SoA)), AND
    b. One blood/plasma sample for anti -PEG, anti-PEG IgM and IgE (only for the central lab).
4. Discontinue study intervention and resume prophylaxis treatment with prior FVIII product.
5. Schedule a follow-up visit (early discontinuation visit) within 4 weeks after the event
    a. For assessment of general well- being of the study participant
    b. To perform assessments for early discontinuation of study participation as per SoA (Section 1.3 SoA) including evaluation of FVIII inhibitor and anti-PEG, anti-PEG IgM, IgE (only for the central lab) and excluding factor VIII recovery and in-hospital infusion of study intervention.

B: If the event of a hypersensitivity reaction occurring while study participant is not under medical supervision at study site (e.g., at home), the following is to be done:

1. Participants should seek prompt medical attention in case of occurrence of any symptom of hypersensitivity reactions and inform the investigator or site staff.

    If treatment of hypersensitivity reaction occurs at the study site, then follow the steps outlined in in “A” above.

    If treatment of hypersensitivity reaction occurs outside the study site, then follow the steps below:

    2. Discontinue study intervention and resume prophylaxis treatment with prior FVIII product
    3. Schedule a visit to the study site within 4 days of the reported event for
        a. Assessment of general well- being of the study participant
        b. AE review.

    At this visit obtain:

        c. Two blood/plasma samples each for FVIII level and FVIII inhibitor (1 for local lab and one for central lab), AND
        d. One blood/plasma sample for anti-PEG, anti-PEG IgM and IgE (only for the central lab)

    4. Schedule a second follow-up visit (early discontinuation visit) approx. 4 weeks after the last visit (see step 3)
        a. For assessment of general well- being of the study participant, AND

b. Perform assessments for early discontinuation of study participation as per SoA (Section 1.3 SoA) including evaluation of FVIII inhibitor and anti-PEG, anti-PEG IgM, IgE (only for the central lab) and excluding factor VIII recovery and in-hospital infusion of study intervention.

For study participants that have discontinued study drug, FVIII level and FVIII inhibitor tests must be done after a sufficient wash-out period depending on the FVIII product the participant is receiving – at least 48 hours or 72 hours for SHL and EHL FVIII products respectively.

8.3.8.2 Clinical guidance for loss of efficacy (LoE)

LoE is defined in Section 8.3.8.

In the event of reported LoE of the study intervention, the following is to be done:

1. Schedule a visit within 4 days of the reported event
2. Obtain
    a. Two pre-infusion blood/plasma samples each for FVIII level and FVIII inhibitor (1 for local lab and one for central lab), AND
    b. One blood/plasma sample for anti-PEG and anti-PEG IgM (for the central lab)
3. Administer BAY 94-9027 (use current prophylaxis dose (IU/kg))
4. Obtain
    a. Two post-infusion blood/plasma samples (1 for local lab and one for central lab) for FVIII level (15-30 min post-infusion)
5. Discontinue study intervention and resume prophylaxis treatment with prior FVIII product if LoE is confirmed by low post-infusion FVIII levels. Inform and discuss with sponsor.
6. Schedule a second follow-up visit (early discontinuation visit) approx. 4 weeks after the last visit (see step 1)
    a. For assessment of general well- being of the study participant
    b. Perform assessments for early discontinuation of study participation as per SoA (Section 1.3 SoA) including evaluation of FVIII inhibitor and anti-PEG, anti-PEG IgM (only for the central lab) and excluding factor VIII recovery and in-hospital infusion of study intervention.

8.3.8.3 Assessment of Severity of AESI

All AESIs will be graded for severity according to CTCAE version 5.0. If no exact matching code is available in CTCAE version 5.0, then use the following guide:

Grade refers to the severity of the AESI. The CTCAE displays Grades 1 through 5 with unique clinical descriptions of severity for each AE based on this general guideline:

- **Grade 1** Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
- **Grade 2** Moderate; minimal, local, or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living (ADL)*

- **Grade 3** Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self care ADL**
- **Grade 4** Life-threatening consequences; urgent intervention indicated
- **Grade 5** Death related to AE

*Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

**Self care ADL refer to bathing, dressing, and undressing, feeding self, using the toilet, taking medications, and not bedridden.

Immune System Disorders					
CTCAE term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Allergic reaction	Systemic intervention not indicated	Oral intervention indicated	Bronchospasm; hospitalization for clinical sequelae; intravenous intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an adverse local or general response from exposure to an allergen. **Navigational note**: If related to infusion, use injury, poisoning and procedural complications: Infusion related reaction. Do not report both.					
Anaphylaxis	-	-	Symptomatic bronchospasm, with or without urticaria; parenteral intervention indicated; allergy-related edema/angioedema; hypotension	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an acute inflammatory reaction resulting from the release of histamine and histamine-like substances from mast cells, causing a hypersensitivity immune response. Clinically, it presents with breathing difficulty, dizziness, hypotension, cyanosis, and loss of consciousness and may lead to death.					

Source: Common Terminology Criteria for Adverse Events (CTCAE), v 5.0, published November 27, 2017), US Department of Health and Human Services

8.3.9 Other Important Events

Anti-drug antibody development

All subjects will be tested for the development of anti-drug antibodies (anti- PEG and anti-PEG IgM). Binding antibodies to PEG will be analyzed in an enzyme-linked immunoassay (ELISA).

In participants who experience LoE, neutralization of activity of BAY 94-9027, observed as lower than expected FVIII recovery, a blood sample should be obtained to test for ADAs (Section 8.2.3.1).

IgE will be analyzed in participants who experience hypersensitivity reactions due to development of ADA.

Development of 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/mL at the central laboratory. If an inhibitor to FVIII is detected after the participant has started treatment with study intervention, the investigator will be notified, and repeat testing within 2 weeks of notification should be obtained. The first positive measurement will be confirmed by a second different sample. After confirmation of the positive result, the inhibitor development will be reported as SAE.

8.3.10 Medical Device Deficiencies

Medical devices approved for use with BAY 94-9027 are being provided for use in this study to facilitate the preparation and infusion of the study intervention. To fulfill regulatory reporting obligations worldwide, the investigator is responsible for the detection and documentation of events meeting the definitions of device deficiency that occur during the study with such devices.

The definition of a medical device deficiency can be found in Section 10.4.3.

Device deficiencies only should be reported to the sponsor, by completing the product technical complaint (PTC) form and submitting the information via the ePTC form or by completing the PTC form and submission to the sponsor via ptc-imp@bayer.com.

NOTE: Deficiencies fulfilling the definition of an AE/SAE will follow the processes outlined in Section 10.4 of the protocol.

8.4 Pharmacokinetics

Detailed PK analysis will not be performed, but FVIII recovery will be assessed frequently as per SoA (Section 1.3).

8.5 Genetics

Genetics are not evaluated in this study.

8.6 Biomarkers

Serum and urinary biomarkers will be measured for assessment of renal safety (Section 10.2).

A limited amount of blood is collected; any remaining amount may be used for additional research on study intervention and/or disease understanding. Blood volume will not be increased for these research purposes.

In addition, further investigations related to the mode of action or the safety of BAY 94-9027 and similar drugs for the treatment of hemophilia may be performed. The same applies to further investigations deemed relevant to hematological diseases and associated health problems. Examples of these investigations include diagnostic, safety, pharmacodynamic, monitoring, or potentially predictive biomarkers.

Results from any additional investigations may be reported separately.

8.7 Immunogenicity Assessments

See Section 8.3.8 and Section 8.3.9 . Immunogenicity will be assessed by measurement of FVIII inhibitors, anti-PEG and anti-PEG IgM antibodies.

For participants who present a hypersensitivity reaction, IgE antibodies to BAY 94-9027 will be measured after the occurrence of the reaction. In case BAY 94-9027 reactive IgE antibodies were detected, specificity toward the FVIII or PEG moiety will be confirmed.

8.8 Health Economics

Health economics parameters are not evaluated in this study.

9. Statistical Considerations

The statistical analysis plan will be finalized prior to first participant first visit and it will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the most important endpoints including primary and key secondary endpoints.

9.1 Statistical Hypotheses

Hypothesis testing is not planned for this study. Based on a Bayesian analysis for the primary endpoint, the posterior probability that the true incidence for an AESI is <5% will be estimated.

9.2 Analysis Sets

Participant Analysis Set	Description
Safety analysis set (SAF Part A)	A participant will be included in the SAF part A if he is enrolled into the part A of the study and has taken at least 1 dose of the study intervention.
Modified Safety analysis set (mSAF Part A)	A participant will be included in the mSAF part A if he is enrolled into the part A of the study and has taken up to 4 doses of the study intervention and does not discontinue study for other reason than an AESI before the fourth ED regardless of emergency use of other FVIII medication.
Modified Intent-to-treat analysis set (mITT Part A)	A participant will be included in the mITT part A if he is enrolled into the part A of the study, has taken at least 1 dose of the study intervention, and has subsequent data for infusions/bleeds documented in the EPD.
Safety analysis set (SAF Part B)	A participant will be included in the SAF part B if he is enrolled into the part B of the study and has taken at least 1 dose of the study intervention in Part B.
Modified intent-to-treat analysis set (mITT Part B)	A participant will be included in the mITT part B if he is enrolled into the part B of the study, has taken at least 1 dose of the study intervention in Part B, and has subsequent data for infusions/bleeds documented in the EPD

9.3 Statistical Analyses

9.3.1 General Considerations

Descriptive statistics will be used for all statistical analyses. The primary endpoint will be analyzed for part A. Secondary endpoints for the primary and secondary objectives will be analyzed for parts A, and B. More details will be provided in the statistical analysis plan.

Assessment of safety will be performed based on the safety analysis set.

Assessment of efficacy will be performed based on the modified ITT analysis set.

9.3.2 Primary Endpoint(s)/Estimand(s) Analysis

See Section 3 for a description of the primary endpoint and estimand.

The mSAF for part A analysis set will be used in this analysis, see Section 9.2. As described in Section 3, the primary estimand targets the stratum of participants who do not discontinue treatment with BAY 94-9027 for other reason than an AESI before the fourth ED regardless of emergency use of other FVIII medication.

Due to the expected low incidence of AESIs (Santagostino et al. 2020), a Bayesian approach will be used for analysis of the primary endpoint.

The 25 participants from age group 7 to <12 years of PROTECT KIDS study with 0 AESIs will be combined with the *n* participants and AESIs from this study for the analysis of the probability of an AESI (*p*), with a total observed sample size of 25 + *n* = N. The Bayesian model for the analysis is then specified as follows:

$r_i \sim$ Bernoulli (p): occurrence of an AESI in participant i , i = 1,… , N;

$p \sim$ Beta(1/4,1/4); prior for the probability of an AESI.

The choice of the neutral prior Beta (1/4,1/4) is to avoid over influence of the prior and limit the degree of polarization of the prior toward 0 and 1. The posterior distribution based on the pooled data will then be Beta(x+1/4,N-x+1/4), where x is the number of participants in the pooled data who experience an AESI.

To note, the above analysis by first pooling in the 25 participants from PROTECT KIDS prior to the Bayesian analysis is equivalent to treating the 25 participants with 0 AESIs as historical data and updating the initial prior Beta(1/4,1/4) to be Beta(0+1/4,25+1/4) as the updated prior for the analysis of participants from this study alone.

The safety of BAY 94-9027 will be characterized by the resulting posterior distribution for the probability of AESI, including its mean, median, mode, and 90% two-sided credible intervals. The posterior probability that the incidence of AESI is <5% will be derived.

9.3.3 Secondary Endpoint(s)/Estimand(s) Analysis

9.3.3.1 Analysis of Secondary Endpoints for the Primary Objective

To further address the primary objective, the following secondary endpoints will be analyzed:

- Adverse drug reactions (ADRs)
- Anti-drug antibody (ADA) development
- Inhibitor development

The analyses for these 3 endpoints will be based on the SAF part A and SAF part B analysis sets, see Section 9.2 for details.

Adverse drug reactions

The number and proportion of participants with any ADRs will be presented.

Anti-drug antibody response

The number and proportion of participants with anti-drug antibodies will be presented along with by-participant listings for ADA responses.

Inhibitor development

The number and proportion of participants with confirmed FVIII inhibitors will be presented by titer (low titer: < 5 BU/mL, high titer: ≥ 5 BU/mL) along with by-participant listings for all measurements of FVIII inhibitors. Note that only inhibitors confirmed by a second positive measurement will be considered positive in the analysis, see Section 8.3.9. The listing will show all results.

9.3.3.2 Analysis of Secondary Endpoints for the Secondary Objective

To address the secondary objective, the following secondary endpoints will be analyzed.

- Number of bleeds per individual observation period of continuous prophylactic treatment to assess (annualized) bleeding rates
- BAY 94-9027 consumption
- Number of infusions/month and year (Annualized Infusion Rate)

The analyses for these 3 endpoints will be based on the modified ITT analysis sets for Part A and Part B of the study, respectively, see Section 9.2 for details.

Bleeding rates

As described in Section 3, the estimand targets the stratum of participants who receive continuous prophylaxis treatment with BAY 94-9027 for at least 3 months without development of an inhibitory antibody to FVIII or ADA that neutralizes activity sufficiently to interfere with effective treatment. The subset of participants in the modified ITT analysis set fulfilling this condition will be used for estimation.

For each participant, the number of bleeds will be related to the individual observation period to assess bleeding rates. Bleeding rates will be annualized at the individual participant level using the formula:

ABR = (number of bleeds * 365.25)/(the available period in the study in days).

Descriptive statistics (N, mean, median, standard deviation, range, Q1, and Q3) will be used to summarize the derived annualized bleeding rates on a group level.

ABRs will be presented for the following types of bleedings:

- Annualized total bleeding (sum of spontaneous bleeds and trauma bleeds) rate
- Annualized spontaneous bleeding rate
- Annualized trauma bleeding rate
- Annualized joint bleeding rate

In addition, model-based estimates for the bleeding rates will be derived using a Negative Binomial model, where y_i denotes the number of bleeding episodes occurring during the time period t_i (possibly differing time periods of follow-up) for participant $i, i = 1, \ldots, n$. Assume that Y_i follows a Negative Binomial distribution with mean μ_i and a common dispersion parameter α. Then μ_i can be modeled as

$$\log \mu_i = \log t_i + \beta_0 \quad ,$$

We thus have

$$\log \mu_i = \log t_i + \beta_0 \Leftrightarrow \frac{\mu_i}{t_i} = \exp(\beta_0).$$

With an estimate for the parameter β_0 the mean rates of events per time unit can be estimated via $\exp(\beta_0)$. This estimate will be provided with its 95% confidence interval.

Determination of Bleeding Count:

Bleeds occurring on the same calendar day will be counted as one bleeding episode with aggregated bleeding sites. A spontaneous joint or spontaneous muscle bleed reported within 72 hours after an identical bleed at the same site or infusion for such a bleed will not be counted as new bleed. Infusions for such bleeds will be considered to be follow-up infusions. (Srivastava et al. 2020)

BAY 94-9027 consumption

Summary statistics for BAY 94-9027 consumption will be provided for prophylaxis treatment, for treatment of bleeds, and overall. Consumption per year and per infusion will be presented based on total dose (IU) and dose per body weight (IU/kg).

Number of infusions/month and year (Annualized Infusion Rate)

Descriptive statistics (N, mean, median, standard deviation, range, Q1, and Q3) for the number of infusions, number of infusions per month, and annualized infusion rate will be presented.

9.4 Interim Analysis

An interim analysis within a group sequential or adaptive design is not planned. Analysis of Part A will be conducted after the last participant completes Part A.

A first analysis of Part B data will be conducted after all participants complete at least 6 months of Part B. A final analysis will be done at the end of the study.

9.5 Sample Size Determination

The selection of the sample size of 30 is based on the assumption that less than 5% of participant out of 30 will experience an AESI and that the data will be pooled with 25 participants from the age group of 7 to <12 years of study 15912 (PROTECT KIDS; NCT01775618) for analysis of the incidence of AESIs. Additional participants may be enrolled in the event of treatment discontinuation during the first 4 EDs of Part A for reasons other than AESI. The study would strive for a balance between age group 7 to <9 years and 9 to <12 years.

A Bayesian Beta-binomial model with each participant having an AESI as a Bernoulli response and a neutral prior probability distribution Beta (1/4,1/4) is used. The choice of the

neutral prior Beta (1/4,1/4) is to avoid over influence of the prior and limit the degree of polarization of the prior toward 0 and 1.

Under these assumptions, the posterior probability that the true incidence for an AESI is <5% will be > 90%.

Details are described by the following scenarios:

- If no participant out of 30 from the new study experience an AESI, then with the Bayesian analysis mentioned above, it is calculated that the median of the posterior distribution of the true incidence of AESI is <0.1% and there is >99% posterior probability that the true incidence of AESI is <5%.
- If 1 participant out of 30 from the new study experience the AESI, it is calculated by a Bayesian Beta-binomial inference with a prior of Beta (1/4,1/4) for the pooled 55 participants that the median of the posterior distribution of the true incidence of AESI is 1.7% and there is 91% posterior probability that the true incidence of AESI is <5%.
- If 2 participants out of 30 from the new study experience the AESI, then the median of the posterior distribution of the true incidence of AESI is 3.5%, and there is 71% posterior probability that the true incidence of AESI is <5%.
- If 3 participants out of 30 from the new study experience the AESI, then the median of the posterior distribution of the true incidence of AESI is 5.4%, and there is 46% posterior probability that the true incidence of AESI is <5%.

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 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 ICH Good Clinical Practice (GCP) guidelines
    - Applicable laws and regulations
- The protocol, protocol amendments, ICF, IB, 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. Any substantial modification of the protocol will be submitted to the competent authorities as substantial amendments for approval, in accordance with ICH GCP and national and international regulations.
- Protocols and any substantial amendments to the protocol will require health authority approval prior to initiation 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

The investigator will be responsible for reporting cases of suspected child abuse and/or neglect according to local regulations including local medical association (e.g., American Academy of Pediatrics, EU Academy of Pediatrics) or Health Department guidelines.

10.1.2 Financial Disclosure

Investigators and sub-investigators 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 and Assent Process

- The investigator, or a person designated by the investigator, will provide the legal guardian (refer to Appendix 10.4 Abbreviations and Definitions) with the written ICF and the participant with the assent if applicable. They must be informed that participation is voluntary. The legal guardian will be required to sign written consent, and the participant if applicable will be required to sign written assent, that meets the requirements of 21 CFR 50, local regulations, International Council on Harmonisation (ICH) guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study center after the nature of the study has been fully explained and before performance of any study-related activity.
- Assent requirements for pediatric participants may vary across regions and countries; local regulations should be followed as appropriate. Assent should be obtained from participants, depending on their age and intellectual status and according to local practice.
- The medical record must include a statement that written informed consent from the legal guardian and assent from the pediatric participant (if deemed appropriate by local ethics review or local regulations) were obtained before the participant was enrolled in the study and the date the written consent and assent were obtained. The authorized person obtaining the informed consent must also sign the ICF and assent form attesting that the pediatric participant did not show signs of dissent particularly in those studies including toddlers and small children; it should be written in language appropriate to the child's developmental and functional status.
- Participants and their legal guardian must be re-consented and re-assented to the most current version of the ICF(s) during their participation in the study.
- Minor participants who assent to a study and later withdraw that assent should not be maintained in the study against their will, even if their legal guardian still wants them to participate.
- A copy of the informed consent and assent forms must be provided to the participant and the participant's legal guardian.
- As appropriate, participants may be given the opportunity to meet privately with a member of the site staff to ask confidential questions and to decline assent for confidential reasons, which, at their request, would not be shared with their legal guardian, unless required by local law.
- There will be no attempt to recontact the participant at adulthood. However, the participant retains the right to withdraw assent/consent for storage of samples unless specified.
- Stored samples will be coded throughout the sample storage and analysis process and will not be labeled with personal identifiers. Participants may withdraw their consent/assent for their samples to be stored for research.

10.1.4 Data Protection

- Participants will be assigned a unique identifier by the sponsor. Any participant records, datasets or biological samples 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/her 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 who will be required to give consent for their data to be used as described in the informed consent.
- 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 2, 3 and 4 and Phase 1 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 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 printed or electronic CRFs 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.
- Guidance on completion of CRFs will be provided in the eCRF HelpText on the CRF and/or the eCRF Completion Instructions available online in the electronic data capture system.
- 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, including definition of study critical data items and processes (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 / contracts.

- 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).
- 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 on the CRF or entered 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 and its origin can be found in the Source Data Location List (SDLL) or equivalent.
- The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.
- The sponsor will perform monitoring 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.

10.1.8 Study and Site Start and Closure

First Act of Recruitment

The study start date is the date on which the first participant is recruited.

Study/Site Termination

The sponsor or 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:

For study termination:

- Discontinuation of further study intervention development

For site termination:

- 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 or no recruitment (evaluated after a reasonable amount of time) of participants by the investigator
- Total number of participants included earlier than expected.

Stopping rules

In addition, the trial will be stopped if any of the following study intervention related events occurs:

- One case of anaphylaxis (CTCAE version 5.0, Grade 3 or higher) or
- One case of severe hypersensitivity/allergic reaction (CTCAE version 5.0, Grade 3 or higher)

If the study is prematurely terminated or suspended, the sponsor shall promptly inform the investigators, the IECs/IRBs, the regulatory authorities, and any contract research organization(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the participant and should assure appropriate therapy and/or follow up.

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.
- Local laboratory results are required as outlined in the SoA (Section 1.3) or in the event that the central laboratory results are not available in time for either study intervention administration and/or response evaluation. If a local sample is required, it is important that the sample for central analysis is obtained at the same time. See Section 8.3.8 for more details regarding local or central laboratory test in

the case of an AESI. Additionally, if the local laboratory results are used to make either a study intervention decision or response evaluation, the results must be recorded, and validated assays must be used. For determination of FVIII levels after infusion of BAY 94-9027, the use of a suitable and validated one-stage or chromogenic assay is crucial.

- 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.

Table 10–1: Protocol-required Safety Laboratory Tests

Laboratory Tests	Parameters
Hematology	Platelet count
	Red blood cell (RBC) count
	White blood cell (WBC) count with differential (neutrophils, lymphocytes, monocytes, eosinophils, basophils)
	Hemoglobin
	Hematocrit
Chemistry	Serum: Creatinine, AST, ALT, Na, K, CO_2, Cl, BUN, total bilirubin, renal serum biomarkers (will include e.g., cystatin C, Lipocalin-2)
Urine	Urinary biomarkers (will include e.g., total protein, albumin, βeta-2 microglobulin, Kidney Injury Molecule-1 (KIM-1), Lipocalin-2)
Immunogenicity	• FVIII inhibitor (see Section 8.3.9) • Anti-drug antibodies (anti-PEG antibodies and anti-PEG IgM antibodies) • IgE antibodies in participants with a hypersensitivity reaction
Other tests	• FVIII levels (one-stage assay at Visit 1 or chromogenic assay thereafter) • Quantitative PEG measurement • vWF (only at Visit 2, pre-infusion)

Investigators must document their review of each laboratory safety report.

10.3 Appendix 3: AEs and SAEs: Definitions and Procedures for Recording, Evaluating, Follow up, and Reporting

10.3.1 Definition of AE

AE Definition

- An AE is any untoward medical occurrence in a clinical study participant, associated with the use of study intervention, whether or not considered related to the study intervention.
- NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) associated with the use of study intervention.

Events Meeting the AE Definition

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (i.e., not related to progression of underlying disease).
- 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 intervention-intervention 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 LoE will be reported as an AESI (either non-serious or serious, if they fulfill the definition of an AE or SAE). Lack of efficacy or failure of expected pharmacological action also constitutes an AE or SAE.

Events <u>NOT</u> Meeting the AE Definition

- Any clinically significant abnormal laboratory findings or other abnormal safety assessments that 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

10.3.2 Definition of SAE

An SAE is defined as any untoward medical occurrence that, at any dose, meets the one or more of the criteria listed:

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

- In general, hospitalization signifies that the participant has been admitted (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether hospitalization occurred or was necessary, the AE should be considered serious.
- Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

d. Results in persistent or significant 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) that may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect

f. Other situations:

- Medical or scientific judgment should be exercised by the investigator in deciding whether SAE reporting is appropriate in other situations such as significant medical events that 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 for allergic bronchospasm, blood dyscrasias, convulsions, or development of intervention dependency or intervention 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.
- It is not acceptable for the investigator to send photocopies of the participant's medical records to the Sponsor in lieu of completion of the CRF/required form.
- 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 one of the following categories:
- Mild: Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
- Moderate: Minimal, local, or noninvasive intervention indicated; limiting age-appropriate instrumental ADL. Instrumental ADL refers to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
- Severe: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling, limiting self care ADL. Self care ADL refers to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

Assessment of Causality

- The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE. The investigator will use clinical judgment to determine the relationship.
- 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.
- 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 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/she 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 submitted documents.
- 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 to the Sponsor 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) 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 investigator site file.

SAE Reporting to the Sponsor via Paper Data Collection Tool

- Email transmission of the SAE paper data collection tool is the preferred method to transmit this information to the Sponsor.
- 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 data collection tool within the designated reporting timeframes.
- Contacts for SAE reporting can be found in investigator site file.

10.4 Appendix 4: AEs, SAEs, and Device Deficiencies: Definitions and Procedures for Recording, Evaluating, Follow up, and Reporting

- Both the investigator and the sponsor will comply with all local reporting requirements for medical devices.
- The detection and documentation procedures described in this protocol apply to all sponsor medical devices provided for use in the study. See Section 6.1.1 for the list of sponsor medical devices.

10.4.1 Definition of Medical Device AE

Medical Device AE

- An AE is any untoward medical occurrence in a clinical study participant, users, or other persons, temporally associated with the use of study intervention, whether or not considered related to the medical device provided by the Study Sponsor. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of the medical device. This definition includes events related to the medical device and events related to the procedures involved.

10.4.2 Definition of Medical Device SAE

A Medical Device SAE is any SAE that:
a. Led to death
b. Led to serious deterioration in the health of the participant, that either resulted in: • A life-threatening illness or injury. 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. • A permanent impairment of a body structure or a body function. • Inpatient or prolonged hospitalization, planned hospitalization for a pre-existing condition, or a procedure required by the protocol, without serious deterioration in health, is not considered an SAE. • Medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function. • Chronic disease (MDR 2017/745).
c. Led to fetal distress, fetal death or a congenital abnormality or birth defect

10.4.3 Definition of Device Deficiency

Device Deficiency Definition

- A device deficiency is an inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety, or performance. Device deficiencies include malfunctions, use errors, and inadequacy of the information supplied by the manufacturer.

10.4.4 Recording and Follow Up of AE/SAE/Device Deficiencies

Assessment of Intensity

The investigator will make an assessment of intensity for each AE/SAE/device deficiency reported during the study and assign it to one of the following categories:

- Mild: Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
- Moderate: Minimal, local, or noninvasive intervention indicated; limiting age-appropriate instrumental ADL. Instrumental ADL refers to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
- Severe: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling, limiting self care ADL. Self care ADL refers to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

Assessment of Causality

- The investigator will provide a preliminary assessment of the relationship between the event and the medical devices listed in Section 6.1.1.

Follow-up of AE/SAE/device Deficiency

- 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/SAE/device deficiency as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide the Sponsor with a copy of any postmortem findings including histopathology.
- New or updated information will be recorded in the originally completed form.
- The investigator will submit any updated SAE data to the Sponsor within 24 hours of receipt of the information.

10.4.5 Reporting of AEs/SAEs Related to the Medical Devices

- For any device related SAE: the investigator should complete the Medical Device Incident form and electronically the complementary SAE page in RAVE. The Medical Device Incident form will be sent to the sponsor by email to PV.caseprocessing@bayer.com within 24 hours.

- **For any AE that was assessed as device related:** the investigator should complete the Medical Device Incident form and electronically the complementary AE page in RAVE. The Medical Device Incident form will be sent to the sponsor by email to PV.caseprocessing@bayer.com within 24 hours.

  If the device deficiencies could potentially lead to the death or serious deterioration of health (=serious injury) of the study participant or others, e.g., staff, complete the Medical Device Incident form only and send it to the sponsor by email to PV.caseprocessing@bayer.com.

  For any AE or SAE that occurred with the users or other person the investigator should complete the Medical Device Incident form only and send it to the sponsor via email to PV.caseprocessing@bayer.com within 24 hours.

10.5 Appendix 5: Abbreviations and Definitions

10.5.1 Abbreviations

ABR	annualized bleeding rate
ADA	anti-drug antibody
ADL	activities of daily living
ADRs	adverse drug reactions
AE	adverse event
AESI	adverse events of special interest
ALT	alanine aminotransferase
anti-PEG	anti-polyethylene glycol
AST	aspartate aminotransferase
BLA	biologic license application
BSL	baseline
BU	Bethesda Unit
CIOMS	Council for International Organizations of Medical Sciences
CONSORT	Consolidated Standards of Reporting Trials
COX-2	cyclooxygenase-2
CRF	case report form
CTCAE	Common Terminology Criteria for Adverse Event
CVAD	central venous access device
DREs	disease-related events
ECG	electrocardiogram
eCRF	electronic case report forms
ED	exposure day
EHL	extended half-life
ELISA	enzyme-linked immunoassay
EPD	electronic patient diary
EV	extension visit
FVIII	Factor VIII
GCP	Good Clinical Practice
Haemo-QoL	Haemo-QoL Kids Short Form (8-16 years old version)
HIPAA	Health Insurance Portability and Accountability Act
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council on Harmonization
IECs/IRB	Independent Ethics Committee/ Institutional Review Board
IgE	immunoglobulin E
IgM	immunoglobulin M
IP	in-person visit
ITT	intent-to-treat

IU	International Units
IV	intravenous
IxRS	interactive voice/web randomization system
LoE	loss of efficacy
MAA	marketing authorization application
mITT	modified intent-to-treat
mSAF	modified Safety analysis set
PEG	polyethylene glycol
PK	Pharmacokinetics
PMS	post-marketing surveillance
PROs	patient-reported outcomes
PTC	product technical complaint
PTPs	previously treated patients
PUPs	previously untreated patients
QoL	Quality of Life
RBC	red blood cell
rFVIII	recombinant FVIII
SAE	serious adverse event
SAF	safety analysis set
SCR	screening
SDLL	Source Data Location List
SHL	standard half-life
SmPC	Summary of Product Characteristics
SoA	Schedule of Activities
SUSARs	suspected unexpected serious adverse reactions
USPI	US prescribing information
WBC	white blood cell
WFH	World Federation of Hemophilia

10.5.2 Definitions

Term	Definition
Study intervention	BAY 94-9027
Legal guardian	Parent(s) (preferably both if available or as per local requirements), legally appointed guardian(s), or legally acceptable representative(s), as defined by national and local laws and regulations, who consent(s) on behalf of the minor. For the purposes of this study, all references to informed consent and assent refer to the pediatric participant (child) and his or her legal guardian who have provided consent (and assent as applicable) according to the Informed Consent Process and Assent Form described in Section 10.1.3 Informed Consent and Assent Process
Caregiver	Delegated primary caregiver(s) who will be responsible for ensuring the study activities are conducted per protocol, e.g., accompany the participant to the study site on each assessment day according to the SoA; consistently and consecutively be available to provide information on the participant using the rating scales during the scheduled study visits; accurately and reliably dispense study intervention as directed; help the study site personnel ensure follow up. This person may be the legal guardian, or another appropriate person, delegated by the legal guardian
Pediatric participant	Persons with hemophilia A younger than 18 years of age participating in research study

10.6 Appendix 6: Protocol Amendment History

The Protocol Amendment Summary of Changes Table for the current amendment is located directly before the table of contents.

Amendment 1: 25 MAY 2022

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.

Overall Rationale for the Amendment

The amendment introduces an additional year of prophylactic treatment with Jivi® culminating in a total of 2 years treatment duration in children of 7-<12 years of age. This prolongation will allow for generation of long-term data planned to be pooled with long-term data from PROTECT KIDS (study 15912; NCT01775618) and support label extension in the pertaining age group.

Furthermore, the treatment prolongation offers sustained study drug provision for 2 years and avoid unnecessary switches of responder patients to other approved FVIII products.

Section # and Name	Description of Change	Brief Rationale
Title Page	Substance name added.	Substance name and compound number used throughout the protocol.
	Acronym added.	Current study acronym was not in use at the time of the original protocol.
	Registry ID removed.	Text was erroneously included in the original protocol.
	Name of Global Clinical Leader changed.	Changed to reflect current team responsibilities.

Document History Table	New section created to summarize all amendments to the original protocol.	Full document history listed including version numbers and dates for each protocol version added for clarity and completeness.
Protocol Amendment Summary of Changes Table	New section added.	This section was added in this protocol amendment to explain the rationale of the amendment and summarize the changes made to the original protocol.
1.1 Synopsis	Rationale updated to include long-term safety.	Extension of the study resulting in a total treatment duration of 2 years will generate long-term safety data
	Objectives and endpoints updated to include a cross-reference to Section 3.	Added to clarify that only primary and secondary objectives and endpoints are described in the synopsis, but the full list of objectives and endpoints is available in Section 3.
	Duration of extension study (Part B) described in the short summary increased from 6 months to 18 months.	Study prolongation will provide treatment to patients for 2 years and avoid unnecessary switches of responder patients to other approved FVIII products.
	Cross-reference in footnote to objectives and endpoints table corrected.	Cross-reference in original protocol pointed to the wrong section.
1.2 Schema	Schema updated to reflect change in duration for the extension study (Part B) from 6 to 18 months.	Change reflects treatment prolongation.
1.3 Schedule of Activities (SoA)	Schedule of assessment for Part A (Table 1-1) revised to include PEG quantification, Urine / serum biomarkers for renal safety, and neurological assessment at Visit 2 and Visit 11. Footnote added for each of these assessments at Visit 2 added stating that the assessments can be performed at a visit other than baseline if the participant is enrolled before Amendment 1 is implemented.	Added PEG-related safety assessments specifically associated with the long-term use of pegylated FVIII products.
	Footnote added to Schedule of assessment for Part A (Table 1-1) clarifying procedures for the early discontinuation visit for participants with adverse events of special interest (AESI).	In-hospital infusion not performed at early discontinuation visits for adverse events of special interest (hypersensitivity or loss of efficacy).
	Return used /unused study intervention at Visit	Visit 6 can be an in-person visit or a

	6 removed from Schedule of assessment for Part A (Table 1-1).	phone call, therefore participants were provided with a study intervention supply sufficient to last through Visit 7. Participants who attend an in-person visit for Visit 6 should return study intervention at Visit 7.
	Footnote added to Schedule of assessment for Part A (Table 1-1) and Part B (Table 1-2) with a cross-reference to Section 10.2.	Cross-reference added to direct to full details on clinical laboratory parameters.
	Schedule of assessment for Part B (Table 1-2) revised to reflect increase in duration from 6 months to 18 months. Monthly visits for Months 13 – 24 added.	Change reflects increase in duration.
	Schedule of assessment for Part B (Table 1-2) revised to include PEG quantification, Urine / serum biomarkers for renal safety, and neurological assessment at Visit 18.	Added PEG-related safety assessments specifically associated with the long-term use of pegylated FVIII products
	Footnotes in Schedule of assessment for Part A (Table 1-1) and Part B (Table 1-2) relabeled.	Footnote labels revised to reflect additions and revisions to original schedules of assessments
2.1 Study Rationale	Text revised to reflect addition of long-term safety assessments.	Study prolongation will allow generation of long-term safety data.
2.3.1 Risk Assessment	Text regarding potential class risk of pegylated FVIII replacement products and previous experience with Jivi® added.	Potential class risk for pegylated FVIII replacement products following long-term treatment added as determined by EMA. From Jivi's preclinical and long-term clinical program no PEG-related safety observations associated with long-term use of Jivi were reported.
3 Objectives, Endpoints, and Estimands	Other objectives revised to include investigation of long-term safety and associated endpoints.	Revised to reflect prolongation of study duration and addition of long-term safety-related measurements.

	Other objectives revised to clarify that Patient-Reported Outcomes questionnaires are used to assess health-related quality of life, not biomarkers.	In the original protocol, patient-reported outcomes were incorrectly grouped as an endpoint for the biomarkers objective.
	Time period for endpoint of secondary estimand revised.	Revised to reflect prolongation of study duration.
4.1 Overall Design	Duration of extension study (Part B) increased from 6 months to 18 months.	Study prolongation will provide treatment to patients for 2 years and avoid unnecessary switches of responder patients to other approved FVIII products.
5.1 Inclusion Criteria	Inclusion criterion 2 reworded to clarify that FVIII activity does not need to be measured at the time of screening if the participant has reliable prior documentation in clinical records.	Original text was not clear resulting in misunderstandings at study sites.
6.2 Preparation, Handling, Storage, and Accountability	Wording describing provision of instructions for use corrected.	The original wording stating that participants would be provided with the Jivi® prescribing information was incorrect. Participants are provided with instructions for preparation of study intervention, which is based on the prescribing information.
6.8 Concomitant Therapy	Vaccination history revised from complete vaccination history to history of vaccinations received within 2 years of enrollment (including vaccination for COVID-19).	The history of vaccination has been shortened to the last 2 years in order to detect any hypersensitivity (HS) reactions that may have occurred close to the time of enrollment in the study. History of COVID-19 vaccination has been added as these vaccines contain PEG moieties which could have triggered HS reactions
	Prior use of pegylated medications added to the list of concomitant medication information collected.	History of chronic use of pegylated products is needed in order to record other medications containing PEG moieties that might confound long-term PEG-related safety events
8.2 Safety Assessments	Anti-drug antibodies and long-term safety assessments added to the list of safety assessments performed for the study.	Anti-drug antibodies added as they were originally missing Safety assessments added to assess the long-term use of pegylated FVIII products.
	Redundant mention of adverse events removed from the list of safety assessments performed for the study.	Adverse events are already covered under the first bullet in the list of safety assessments.
8.2.1 Physical Examination	Neurological assessment added to the description	Neurological assessment added as part of the PEG-related safety assessments

	of physical examinations performed during the study.	to investigate the potential long-term Jivi® safety.
8.3.8 Adverse Events of Special Interest (AESI)	Description of number of blood samples for AESIs corrected.	One blood/plasma sample is sufficient to measure anti-PEG, anti-PEG IgM, and IgE. Original wording described collection of a distinct sample for measurement of IgE.
	Description for the follow-up (early discontinuation) visit for AESI events revised for clarity. Wording for assessments performed at this visit changed to emphasize measurement of FVIII inhibitor and anti-PEG IgM at this visit and clarify that factor VIII recovery and in-hospital infusion of study intervention should not be performed for participants reported with AESIs.	Language added to clarify that the follow-up visit 4 weeks after the AESI is the early discontinuation visit for participants with AESIs.
8.4 Pharmacokinetics	Removed reference to Section 8.3.6.	Reference was erroneously included in the original protocol.
8.6 Biomarkers	Reference to serum and urinary biomarkers in Section 10.2 added.	Serum and urinary biomarkers added in this amendment as PEG-related safety assessments specifically associated with the long-term use of pegylated FVIII products.
9.4 Interim Analysis	Analysis plan for Part B revised to reflect increase in duration. Analysis of Part B to be conducted at Month 6 in addition to the analysis at the end of the study.	Due to the increase in Part B duration from 6 months to 18 months, the plan to evaluate efficacy and safety of the 5-day regimen during the first 6 months of Part B has not been changed; therefore, the Month 6 analysis has been added in addition to the analysis at the end of the study.
10.2 Appendix 2: Clinical Laboratory Tests	Serum chemistry parameters added.	Added PEG-related safety assessments specifically associated with the long-term use of pegylated FVIII products
	Urinary parameters added.	
	For other tests, quantitative PEG measurement and vWF added. Text describing measurement of FVIII revised to clarify that a one-stage assay is used only at Visit 1.	
10.4.5 Reporting of AEs/SAEs related to the Medical Devices	Removed all instances of the word “manually” from instructions for completion of the Medical Device Incident form.	Medical Device Incident form is completed electronically. Original language was causing misunderstandings at study sites.

11 References	Two new references added. Outdated reference removed.	References adapted based on edits made in Section 2.3.1 Risk Assessment.
Throughout	Minor editorial and document formatting revisions.	Minor changes were made to correct typos, grammar, document headers, etc. have been made throughout the document. These minor changes are not individually summarized.

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