Document Type:	Study Protocol
Official Title:	A Post Approval Commitment study to evaluate the efficacy, safety, and pharmacokinetics of KOVALTRY in Chinese children, adolescents /adults with severe hemophilia A
NCT Number:	NCT04565236
Document Date:	12-MAY-2023

Title Page

Protocol Title: **A Post Approval Commitment study to evaluate the efficacy, safety, and pharmacokinetics of KOVALTRY in Chinese children, adolescents/adults with severe hemophilia A.**

Protocol Number: 19855

Amendment Number: Amendment 2

Protocol Version: 4.0

Compound Number: KOVALTRY (No. BAY 81-8973)

Study Phase: Phase IV

Short Title: KOVALTRY Efficacy, Safety, and PK Study in Chinese hemophilia A patients.

Sponsor Name: Bayer Healthcare Company Limited

Legal Registered Address: No.7 Rong Jing East Street BDA, Beijing, China

Regulatory Agency Identifier Number(s):

CHINA IDL (Imported Drug License) Number: CCI
(corresponding strength for 250IU, 500IU & 1000 IU)

Protocol Amendment Date: 12 MAY 2023

Name: PPD, 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.

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

Document History Table

DOCUMENT HISTORY			
Document	**Version**	**Date**	**Comments (if applicable)**
Amendment 2 (Global)	4.0	12 MAY 2023	Version 3.0 (dated 12 OCT 2022) was obsoleted.
Amendment 1 (Global)	2.0	22 OCT 2020	
Original Protocol	1.0	29 JAN 2020	

Amendment 2 (12 MAY 2023)

Overall Rationale for the Amendment:

Protocol Amendment Summary of Changes Table

Section Number and Name	Description of Change	Brief Rationale
Section 1.1 Synopsis Section 1.3.2 Part B (PUPs/MTPs) SoA Section 4.1 Overall Design Section 5.1.2 Part B (PUPs/MTPs) Inclusion Criteria Section 6.8.3 Participant Discontinuation/Withdrawal from the Study Section 7.2.2 Visit 2/Baseline (No Later Than 4 Weeks From Visit 1) Section 7.3.2 Incremental Recovery of KOVALTRY Section 8 Safety Assessments Section 8.10.2 Part B (PUPs/MTPs) Immunogenicity Assessments Section 10.2 Appendix 2: Clinical Laboratory Tests Section 10.5.2 Optional ITI Treatment - Schedule of Activities	Change all the assays planned in central lab to local lab for Part B.	According to the approved KOVALTRY label, FVIII levels can be measured in plasma with a one stage coagulation assay as well as with a chromogenic assay using the routine methods of the local laboratory. In addition, it will shorten the turnover time of lab report.
Section 1.1 Synopsis Section 1.3.2 Part B (PUPs/MTPs) SoA Section 4.1.2 Part B (PUPs/MTPs) Section 7.2 Study Visits - Part B (PUPs/MTPs) Section 7.2.2 Visit 2/Baseline (No Later Than 4 Weeks From Visit 1)	Romove the Combined Screening and Baseline (PUPs only) in Part B.	Combined Visit in Part B was designed for PUPs to avoid unnecessarily prolonged screening period due to 5-7 days turnover from central lab. Since local lab will be adopted, PUPs can be randomized shortly after Visit 1.
Section 1.3.2 Part B (PUPs/MTPs) SoA Section 7.2.2 Visit 2/Baseline (No Later Than 4 Weeks From Visit 1)	Remove FVIII trough level assessment from Visit 2 in Part B.	For PUPs, retesting of FVIII trough level in Visit 2 is not necessary becasuse it will be evaluated and documented in Visit 1 which is just shortly

		before Visit 2. For MTPs with longer screening period, the FVIII trough level has already been included in recovery evaluation after randomization.
Section 7.3.2 Incremental Recovery of KOVALTRY	The chromogenic assay was changed to one-stage clotting assay in all plasma concentrations of FVIII measurement for Part B.	The chromogenic assay is not available in local lab and the FVIII:C of KOVALTRY can be measured in plasma with a one-stage coagulation assay as well as with a chromogenic assay using the routine methods of the laboratory.
Section 10.2 Appendix 2: Clinical Laboratory Tests	To indicate that a separate page for local laboratory results will be provided in eCRF for Part B.	A separate page for local laboratory results capturing for Part B should be provided in eCRF since all the assays planned in central lab will be changed to local lab.
Section 1.2 Schema	Change captions for Figure 1.2-1 and Figure 1.2-2 to Figure 1-1 and Figure 1-2.	Technical update.

In addition, editorial and administrative changes have been made throughout the document.

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1. Protocol Summary

1.1 Synopsis

Protocol Title: A Post-Approval Commitment (PAC) study to evaluate the efficacy, safety, and pharmacokinetics of KOVALTRY in Chinese children, adolescents/adults with severe hemophilia A.

Short Title: KOVALTRY Efficacy, Safety, and PK Study in Chinese hemophilia A patients.

Rationale: This study is being done to fulfill a post-approval commitment for KOVALTRY received from the China Center for Drug Evaluation (CDE) and China National Medical Products Administration (NMPA).

The marketing authorization of KOVALTRY in China is based on demonstrated safety and efficacy of KOVALTRY in completed studies in previously treated severe hemophilia A patients (PTPs), which included 29 adult Chinese PTPs. China CDE and NMPA requested additional efficacy, safety, and PK data for KOVALTRY in previously treated Chinese hemophilia A patients as well as previously untreated patients (PUPs). The design, objectives, and endpoints for this study were developed in consultation with China CDE. As agreed with CDE, Part A of this planned study will obtain additional efficacy, safety, and pharmacokinetic data for KOVALTRY in Chinese PTPs (children (<12 years of age) and also adult/adolescents (≥12 years of age)) with severe hemophilia A. Additionally, as per consultation with CDE, Part B of the study will obtain efficacy and safety data in previously untreated/minimally treated Chinese children (<6 years of age) with severe hemophilia A. The results (at least interim) from this Phase IV study will be submitted with the KOVALTRY licensure renewal application in China.

Objectives and Endpoints:

Part A: Efficacy, Safety, and Pharmacokinetics of KOVALTRY in PTPs (Children <12 Years of Age and Adolescents/Adults ≥12 Years of Age)

Objectives	Endpoints
Primary	
Efficacy	
• Evaluate the efficacy of prophylaxis treatment with KOVALTRY in Chinese children (<12 years) and adolescents/adults (≥12 years) with severe hemophilia A	• Annualized bleeding rate (ABR)
Secondary	
Efficacy	
• Evaluate efficacy of KOVALTRY for treatment of bleeding episodes • Assess efficacy within 48 hours of previous prophylaxis infusion • Evaluate the in vivo recovery of KOVALTRY	• Number of infusions needed to achieve hemostasis and response to treatment of bleeds • ABR within 48h of previous prophylaxis infusion • In vivo recovery of KOVALTRY at baseline, 2 months after start of

• Hemostatic control for minor surgeries	study treatment, and study end • Physician assessment of adequacy of hemostasis in minor surgery
Safety	
• Assess the safety of KOVALTRY for prophylaxis and treatment of bleeding episodes in Chinese children (<12 years) and adolescents/adults (≥12 years) with severe hemophilia A	• FVIII inhibitor development by the Nijmegen Bethesda assay • Treatment-emergent adverse events (TEAEs)
Pharmacokinetics	
• Evaluate pharmacokinetics (PK) of KOVALTRY in Chinese children (<12 years) and adolescents/adults (≥12 years to 65 years) severe hemophilia A patients	• PK parameters include C_{max}, AUC, and $t_{½}$

Part B: Efficacy and Safety of KOVALTRY in PUPs/MTPs (Children <6 Years of Age)

Objectives	Endpoints
Primary	
Efficacy	
• Assess the efficacy of KOVALTRY within 48 hours of previous prophylaxis infusion in previously untreated/minimally treated Chinese children (<6 years of age) with severe hemophilia A	• ABR within 48 hours of previous prophylaxis infusion
Secondary	
Efficacy	
• Evaluate the efficacy of prophylaxis treatment with KOVALTRY • Assess the efficacy of KOVALTRY for treatment of bleeding episodes • Evaluate the in vivo recovery of KOVALTRY • Hemostatic control for minor surgeries	• ABR during the prophylaxis period • Number of infusions required to treat a bleed and response to treatment of bleeds • In vivo recovery of KOVALTRY at baseline and study end • Physician assessment of adequacy of hemostasis in minor surgery
Safety	
• Assess the safety of KOVALTRY for prophylaxis and treatment of bleeding episodes in previously untreated/minimally treated Chinese children (<6 years of age) with severe hemophilia A	• FVIII inhibitor development by the Nijmegen Bethesda assay • Treatment-emergent adverse events (TEAEs)

The Sponsor expects the study to provide additional efficacy and safety results to support the results obtained from the completed clinical studies with KOVALTRY (LEOPOLD I, LEOPOLD II, and LEOPOLD Kids Part A) in previously treated severe hemophilia A patients.

Additionally, the Sponsor expects efficacy and safety results in PUPs/MTPs to be in line with that known for the class of FVIII products in this patient population.

Overall Design:

This is a multicenter, uncontrolled, open-label, single arm treatment, 2-part study.

- Part A will assess efficacy, safety, and PK of KOVALTRY in previously treated Chinese children and adolescents/adults with severe hemophilia A (defined as FVIII:C <1% with one-stage clotting assay).
    - 6 months of prophylaxis treatment with KOVALTRY
    - PK assessments are planned in a subset of 12 children, <12 years and 12 adolescents/adults, ≥12 years
- Part B will assess efficacy and safety of KOVALTRY in previously untreated/minimally treated Chinese children with severe hemophilia A (defined as FVIII:C <1% with one-stage clotting assay). Participants will receive treatment with KOVALTRY until at least 50 exposure days (ED) is achieved.

Disclosure Statement: This is an open-label treatment study in previously treated, minimally treated, and previously untreated Chinese children and adolescents/adults with severe hemophilia A.

Intervention Model: Participants are in a single treatment arm for the duration of the study.

Primary Purpose: Treatment

Number of Treatment Groups:

- Part A (PTPs): 1 treatment group with two arms based on age
- Part B (PUPs/MTPs): 1 treatment group

Blinding: No blinding.

Number of Participants:

- Part A of this study plans to enroll a total of 42 previously treated Chinese patients with severe hemophilia A (see Section 5), defined as FVIII:C <1% with one-stage clotting assay.
    - **Children:** 30 males with severe hemophilia A, <12 years with ≥ 50 exposure days (ED) to any FVIII medication (excluding cryoprecipitate and fresh frozen plasma (FFP)), no history of inhibitors, and no other bleeding disorders
    - **Adolescents and Adults:** 12 males ages ≥12 to 65 years with ≥150 ED to any FVIII medication (excluding cryoprecipitate and FFP), no history of inhibitors, and no other bleeding disorders
- Part B of this study plans to enroll approximately 6 Chinese PUPs/MTPs with severe hemophilia A, <6 years of age, with no prior exposure to FVIII product (PUPs) or no more than 1 ED with any purified FVIII concentrate or 3 exposures with FFP or cryoprecipitate (MTPs), no history of inhibitors (MTPs), and no other bleeding disorders.

After signing Informed Consent and/or Assent (or informed consent signed by the participant's parent or legal representative), the participants will be screened to ensure they meet all inclusion and none of the exclusion requirements.

Approximately 50 participants will be screened in order to achieve 42 evaluable participants in Part A. About 10 participants will be screened in order to achieve approximately 6 evaluable participants in Part B.

Intervention Groups and Duration:

The study intervention will be used both for treatment and prevention of bleeding events and with surgical procedures. Individual participant dose decisions are at the discretion of the investigator.

Part A: All participants in Part A are expected to be treated for 6 months.

According to the Prescribing Information for KOVALTRY, dose regimens for prophylaxis are:

- Study participants ≤12 years: 25 to 50 IU of KOVALTRY per kg body weight (given IV) twice weekly, three times weekly, or every other day according to individual requirements for 6 months
- Study participants >12 to 65 years: 20 to 40 IU of KOVALTRY per kg of body weight (given IV) two or three times per week for 6 months

Part B: All participants in Part B are expected to be treated for 50 ED. Treatment in Part B may begin with start of prophylaxis with 15 to 50 IU/kg (minimum dose: 250 IU) at least 1 day a week; alternatively, prophylaxis can be started directly with a once-a-week schedule minimum dose of 250 IU for PUPs/MTPs of any weight. The starting dose may be tailored to the participant's weight or demonstrated bleeding tendency.

Study participants who develop high-titer inhibitor (>5 BU/mL, confirmed by local laboratory) related to study drug, that interferes with effective treatment with FVIII, may opt to enter optional ITI treatment with study drug (Section 10.5.1) or leave the study and be treated with other therapies outside of the study at the discretion of the investigator. The optional ITI treatment with the study drug within the study requires a separate signed informed consent. Refer to Section 10.5 for additional details.

Study Visits:

Part A: Part A will include the following study visits:

- Visit 1: Screening (up to 6 weeks prior to Baseline),
- Visit 2: Baseline (first study drug administration, no more than 6 weeks after completion of the screening assessments),
- Visit 3: (1 month after baseline),
- Visit 4: (2 months after baseline),
- Visit 5: Final visit (6 months after baseline)/Early Termination.

Part B: Part B will include the following study visits:

- Visit 1: Screening,
- Visit 2: Baseline (first study drug administration for MTPs only),
- Visit 3: ~5 ED,
- Visit 4: ~10 ED,
- Visit 5: ~15 ED,
- Visit 6: ~20 ED,
- Visit 7/Interim visit: 30 to 40 ED,

- Visit 8/Final visit (50 ED)/Early Termination.

All participants or parents/caregivers in Part A and Part B will receive a safety follow-up call approximately 2 weeks after the Final visit.

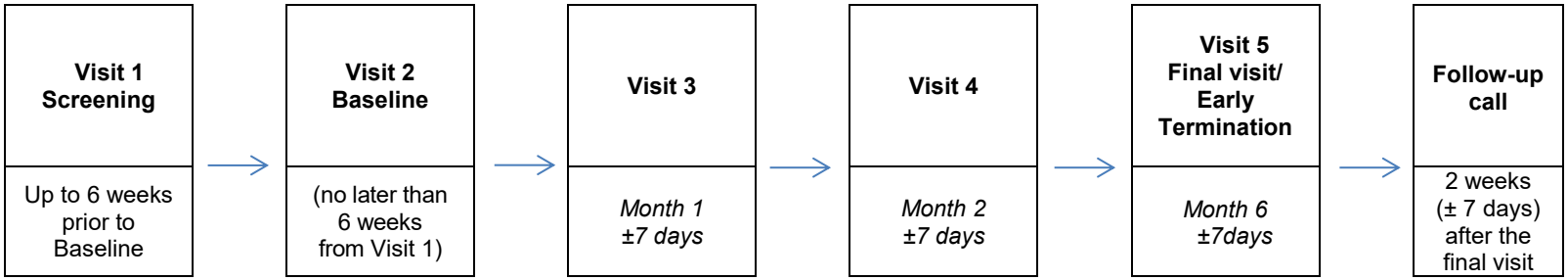
Data Monitoring Committee: No

1.2 Schema

The schema of study visits for Part A is shown in Figure 1–1, and details of the study activities in Part A are displayed in Section 1.3.1.

The schema of study visits for Part B is shown in Figure 1–2, and details of the study activities in Part B are displayed in Section 1.3.2.

Figure 1–1: Part A (PTPs) Study Schema

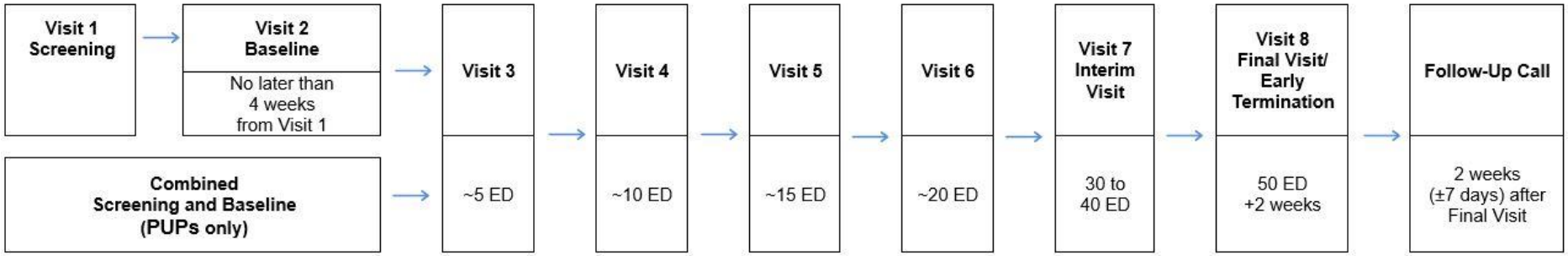


Notes:

Between the scheduled study visits, drug dispensing visits approximately every 28 days (± 7 days) may require participants and/or their caregivers to return to the study center to obtain additional study drug.

Between scheduled visits, participants and/or their caregivers will receive a phone call approximately every 2 weeks between Baseline and Visit 5 (Month 6) from the study center to verify proper completion of the participant diary, to review any new AEs and changes in concomitant medication since the last study visit, to update the status of the participant, respond to any questions, and to confirm the next dispensing and study visits.

Figure 1–2: Part B (PUPs/MTPs) Study Schema



Notes:

Drug dispensing visits will be done in accordance with the individual drug dispensing schedule. Additional drug dispensing visits could be performed between Visit 6 and the Final visit in order to ensure study participants have sufficient study drug to cover the period between the scheduled study visits.

Study center staff will call the participant or parent/caregiver approximately every 2 weeks between Baseline and Visit 8 (Final visit) and approximately 2 weeks after the last visit to verify proper completion of the electronic patient diary, review any new adverse events and changes in concomitant medication since the last study visit, update the status of the participant, respond to any questions, and confirm the next dispensing and study visits.

1.3 Schedule of Activities (SoA)

1.3.1 Part A (PTPs) SoA

Assessment	**Visit 1[a] Screening**	**Visit 2[a] Baseline** (no later than 6 weeks from Visit 1)	**Visit 3[a]** Month 1 ±7 days	**Visit 4[a]** Month 2 ±7 days	**Visit 5[a] Final Visit/ Early Termination** Month 6 ±7days	**Follow-Up Call** +2 weeks (±7 days) after the Final Visit
Screening and enrollment						
Informed consent	X					
Inclusion / exclusion criteria	X	X				
Demographic data	X					
Height and weight[b]	X	X	X	X	X	
Medical, surgical history	X					
Prior medication (medication history)[c]	X					
Physical examination	X	X			X	
FVIII trough level (at least 72 hours after last pre-study FVIII infusion) – one stage assay	X					
Study drug administration (as per prescribed regimen)[d]		Given continuously in accordance with assigned prophylaxis regimen				
Study drug dispensation[d]		X	X	X		
Study drug accountability			X	X	X	
Efficacy						
Electronic patient diary (EPD) training and dispensing[e]	X					
eDiary documentation and review (continuously)[e]		X	X	X	X	
Recovery (FVIII level)[f]		X		X	X	
PK in children <12 years (in a subset of participants)[g]		X				
PK in adolescents/adults ≥12 years[h]		X			X	
Safety						
Adverse events		X	X	X	X	X
Concomitant medication		X	X	X	X	X
Vital signs	X	X	X	X	X	
Serology screening (HBV, HCV, HIV) and CD4 count	X					
Laboratory examination[i]	X	X		X	X	
Blood sample for inhibitor test[j]	X	X	X	X	X	

Assessment	**Visit 1[a] Screening**	**Visit 2[a] Baseline** (no later than 6 weeks from Visit 1)	**Visit 3[a]** Month 1 ±7 days	**Visit 4[a]** Month 2 ±7 days	**Visit 5[a] Final Visit/ Early Termination** Month 6 ±7days	**Follow-Up Call** +2 weeks (±7 days) after the Final Visit
Phone calls[k]						X

Abbreviations: AE = adverse event; CD4 = cluster of differentiation 4; CRF = case report form; EPD = electronic patient diary; FVIII = factor VIII; HBV = hepatitis B virus; HCV = hepatitis C virus; HIV = human immunodeficiency virus; PK = pharmacokinetics; PTP = previously treated patient; RAVE = data base for electronic case report

a. The scheduled study visits are shown in the table. Unscheduled visits are permitted at any time at the discretion of the investigator. In addition, participants may visit the study center approximately every 28 days (± 7 days) for medication supplies and receive phone calls, as outlined below in notes e and k.

b. Height and weight will be obtained for all participants at screening. At all subsequent visits, height and weight will be obtained for children and adolescents. For adults, only weight will be collected after screening.

c. Prior medication will be recorded at screening as part of medical history. Concomitant medication will be recorded at subsequent visits.

d. Study drug will be injected throughout the study in accordance with assigned prophylaxis regimen. Drug dispensing will be done in accordance with the individual drug dispensing schedule every 28 days (± 7 days).

e. The EPD may be given to the participants to take home at any time between Screening and Baseline, but no entries are to be made before the first infusion of study drug at Baseline.

f. Blood samples for FVIII level are to be taken pre-infusion and 15 to 30 minutes after end of infusion to calculate recovery at Visits 2, 4, and 5. Infusion doses for recovery measurements must be given in hospital and directly reported in RAVE. The bioanalysis will be done at a central laboratory.

g. PK evaluation is required only once in a subset of pediatric participants (12 children). Blood samples to be taken at the following time points subsequent to a washout of at least 48 h after last dose of KOVALTRY: pre-infusion, 15 to 30 min, 4 h, and 24 h post-infusion. Exact times need to be entered into CRF. PK evaluation should be done at Visit 2. Infusion doses for PK measurements must be given in hospital and directly reported in CRF. A standard dose of 50 IU/Kg should be given prior to PK evaluation.

h. PK evaluation is required at start and end of treatment in all adolescent/adult participants only (12 adolescent/adults) . Blood samples to be taken at the following time points subsequent to a washout of at least 48 h after last dose of KOVALTRY: pre-infusion, 10 to 15 min, 30 min, 1 h, 4 h, 6 to 8 h, 24 h, and 30 to 48 h post-infusion. Exact times need to be entered into CRF. PK evaluation should be done at Visit 2 and Visit 5. Infusion doses for PK measurements must be given in hospital and directly reported in RAVE. A standard dose of 50 IU/kg should be given prior to PK evaluation.

i. Standard laboratory assessments include hematology and clinical chemistry.

j. The first positive inhibitor test after start of treatment with study intervention must be confirmed by analysis of a second sample and by analysis of FVIII level recovery within 2 weeks of the investigator's notification.

k. Study center staff will call the participant or parent/caregiver approximately every 2 weeks between Baseline and Visit 5 (Month 6) and approximately 2 weeks after the last visit (Visit 5) to verify proper completion of the participant diary and to review any new AEs and changes in concomitant medication since the last study visit.

1.3.2 Part B (PUPs/MTPs) SoA

Assessments	**Visit 1[a] Screening[b]**	**Visit 2[a] Baseline** (no later than 4 weeks from Visit 1)	**Visit 3[a] ED ~5**	**Visit 4[a] ED ~10**	**Visit 5[a] ED ~15**	**Visit 6[a] ED ~20**	**Visit 7[a]/ Interim Visit[c] 30 to 40 ED**	**Visit 8[a]/Final Visit 50 ED[d]/ Early Termination** +2 weeks	**Follow-Up Call[e]** 2 weeks ±7 days after the Final Visit
Screening and enrollment									
Informed consent	X								
Inclusion / exclusion criteria	X	X							
Demographic data	X								
Height/length and weight[f]	X	X	X	X	X	X	X	X	
Medical and surgical history	X								
Prior medications (medication history)[g]	X								
Physical examination	X							X	
FVIII trough level (at least 72 hours after last pre-study FVIII infusion) - one-stage assay	X[h]								
FVIII inhibitor (at least 72 hours after last pre-study FVIII infusion) - one-stage assay	X[h]	X[i]							
Study drug administration (as per prescribed regimen)[j]		Given continuously in accordance with assigned prophylaxis regimen							
Study drug dispensation[j]		X	X	X	X	X	X		
Study drug accountability			X	X	X	X	X	X	
Efficacy									
EPD training and dispensing[k]	X	X							
EPD documentation and review (continuously)		X	X	X	X	X	X	X	
Recovery (FVIII level)[l]		X[m]				X		X	
Safety									
Vital signs	X	X	X	X	X	X	X	X	
Adverse events		X	X	X	X	X	X	X	X
Concomitant medications (continuously)[g]		X	X	X	X	X	X	X	X
Laboratory examination[n]	X								
FVIII inhibitor[o]			X	X	X	X	X	X	

Assessments	**Visit 1[a] Screening[b]**	**Visit 2[a] Baseline** (no later than 4 weeks from Visit 1)	**Visit 3[a] ED ~5**	**Visit 4[a] ED ~10**	**Visit 5[a] ED ~15**	**Visit 6[a] ED ~20**	**Visit 7[a]/ Interim Visit[c] 30 to 40 ED**	**Visit 8[a]/Final Visit 50 ED[d]/ Early Termination** +2 weeks	**Follow-Up Call[e]** 2 weeks ±7 days after the Final Visit
FVIII trough level[o]			X	X	X		X		
Phone calls (biweekly)[p]		X	X	X	X	X	X	X	X

Abbreviations: ED = exposure days; EPD = electronic patient diary; FVIII = factor VIII; ITI = immune tolerance induction; MTP = minimally treated patients; PUP = previously untreated patients; RAVE = data base for electronic case report

a The scheduled study visits are shown in the table. Unscheduled visits are permitted at any time at the discretion of the investigator.
b For MTPs, the Screening visit should only take place after a washout period of at least 72 hours following any previous treatment with any FVIII replacement product.
c This visit is required only for PUPs and MTPs who have less than 40 ED, 6 months after the Baseline visit. The intent is to have at least one scheduled visit between completion of 20 ED and the expected date of accumulating 50 ED. The primary purpose of the visit is to assess the well-being of the participant, ensure continued compliance with the treatment, and make any needed adjustments in dosage or infusion frequency based upon weight or bleeding events.
d For participants who do not develop high-titer FVIII inhibitor, the Final visit can be performed as soon as a minimum of 50 ED is achieved, but no later than 2 weeks after achieving 50 ED.
e This follow-up is not required for study participants who develop high-titer inhibitor and continue in the study in the Optional ITI Treatment (Section 10.5.1).
f Height/length and weight will be obtained for all participants at screening and at all subsequent visits.
g Prior medications will be recorded at screening as part of medical history. Concomitant medications will be recorded at subsequent visits.
h Inhibitor is to be evaluated at screening and in repeat sampling at least 1 week but not more than 2 weeks after screening (local laboratory testing) in MTPs only (i.e., unnecessary to be evaluated in PUPs). For MTPs, FVIII level and presence of FVIII inhibitor should be measured at least 72 hours after the last dose of FVIII. For MTPs, study drug administration should start upon availability of result from local laboratory testing documenting negative inhibitor titer.
i Baseline inhibitor testing will be done in MTPs only.
j Study intervention will be administered throughout the study in accordance with the assigned prophylaxis regimen. Drug dispensing will be done in accordance with the individual drug dispensing schedule. Additional drug dispensing visits could be performed between Visit 6 and the Final visit in order to ensure study participants have sufficient study drug to cover the period between the scheduled study visits.
k The EPD may be given to the parent/caregiver to take home at any time between the Screening and Baseline visits, but no entries should be made before the first infusion of study drug at the Baseline Visit.
l Blood samples for FVIII level will be taken pre-infusion and at 15 to 30 minutes after end of infusion to calculate recovery at the Baseline visit and Visits 6 and 8 (Final visit). Infusion doses for recovery measurements must be given in hospital and directly reported in RAVE. The bioanalysis will be done at a local laboratory.
m For PUPs who do not start treatment with study drug at the Baseline, recovery evaluation should be done at the study visit when prophylaxis is started.
n Standard laboratory assessments include hematology and clinical chemistry. Guidance for blood draws in participants ≤10 kg is provided in Section 10.2.
o Inhibitor will be evaluated at every visit after the start of treatment with study drug for MTPs as well as for PUPs. FVIII level and presence of FVIII inhibitor should be measured at least 48 hours after the last dose of study drug. The first positive inhibitor test after start of treatment with study drug must be confirmed by analysis of a second sample and by analysis of FVIII level recovery within 2 weeks of the investigator's notification.
p Study center staff will call the parents/caregivers of participants approximately every 2 weeks between Baseline and Visit 8 (Final visit) and approximately 2 weeks after the last visit to verify proper completion of the participant diary and to review any new AEs and changes in concomitant medication since the last study visit.

2. Introduction

KOVALTRY (BAY 81-8973), antihemophilic factor (recombinant), is a recombinant, human DNA sequence derived, full length Factor VIII concentrate indicated for use in adults and children with hemophilia A (congenital Factor VIII deficiency). As described in the KOVALTRY Prescribing Information in China (provided as an attachment in Section 12),[1] KOVALTRY temporarily replaces the missing clotting factor VIII needed for effective hemostasis in patients with hemophilia A. Upon activation of the clotting cascade, FVIII is converted to activated FVIII and acts as a cofactor for activated factor IX, accelerating the conversion of factor X to activated factor X on phospholipid surfaces, which ultimately converts prothrombin to thrombin and leads to the formation of a fibrin clot.[1]

The multinational clinical development program for KOVALTRY (LEOPOLD) included 3 clinical studies (LEOPOLD I, LEOPOLD II, and LEOPOLD Kids) that have demonstrated efficacy and safety for preventing and treating bleeding episodes in approximately 240 children, adolescents, and adults with severe hemophilia A across different populations and different regions of the world, including 6 Chinese participants in the LEOPOLD I study (PK evaluation part) and 23 adult/adolescent Chinese patients in the LEOPOLD II study.

KOVALTRY is currently authorized to be marketed in [redacted] countries including China under the proprietary name KOVALTRY.

2.1 Study Rationale

Based on efficacy and safety data from completed multinational studies with KOVALTRY and the consistent results for both PK and clinical efficacy/safety in 29 adult/adolescent patients with severe hemophilia A from China, KOVALTRY was conditionally approved for use in adults and children in China in July 2018 for:

- Routine prophylaxis to reduce the frequency of bleeding episodes
- On-demand treatment and control of bleeding episodes
- Perioperative management of bleeding

Approved dosing recommendations for routine prophylaxis (as prescribing information, Section 12):

- Adolescents and adults: 20 to 40 IU of KOVALTRY per kg of body weight two or three times per week
- Children ≤12 years old: 25 to 50 IU of KOVALTRY per kg body weight twice weekly, three times weekly, or every other day according to individual requirements

Efficacy and safety of KOVALTRY for prophylaxis, treatment of bleeding episodes, and perioperative management of hemophilia A patients were demonstrated in the completed LEOPOLD clinical trials in previously treated severe hemophilia A patients and supported approval for use of KOVALTRY in the management of hemophilia A patients in 49 countries, including China. LEOPOLD I and LEOPOLD II studies included 6 and 23 previously treated Chinese severe hemophilia A patients, respectively. There were no Chinese hemophilia A patients enrolled into LEOPOLD Kids study.

As part of the China NDA post-approval commitment, the China CDE and NMPA requested additional efficacy and safety data in previously treated and previously untreated Chinese hemophilia A patients. As agreed with China CDE, Part A of this study will obtain additional efficacy, safety, and PK data for KOVALTRY in Chinese PTPs (children <12 years of age

and adolescents/adults ≥12 years of age). Additionally, as per consultation with CDE, Part B of the study will obtain efficacy and safety data in Chinese PUPs/minimally treated patients (MTPs [children <6 years of age]).

In the event that the study is not be finalized in time for a report to be delivered for license renewal, an interim analysis will be performed with all available data.

2.2 Background

Hemophilia A is a congenital disorder in which mutations in the FVIII gene lead to a qualitative or quantitative deficiency of FVIII protein and activity resulting in prolonged bleeding after trauma and recurrent spontaneous bleeding episodes.[2] The World Federation of Hemophilia's global survey 2016 (the most recent year for which statistics are available) reported 14,390 cases of hemophilia in China. Of these, 12,533 cases were hemophilia A.[3]

Individuals with severe hemophilia A experience frequent, recurrent bleeding into the soft tissue and joints, resulting in joint damage and debility, and significant negative effects on their Quality of Life (QoL), psychosocial well-being, education, and financial condition.[2, 4, 5]

Standard treatment for hemophilia A patients is the replacement of the missing protein by infusion of exogenous FVIII concentrates, either as plasma-derived FVIII (pdFVIII) or recombinant rFVIII concentrates.[2] FVIII is an important component of normal coagulation, and the biologic behavior is similar across all populations.[6] Treatment is specifically directed to achieve desired plasma FVIII levels. There is a direct correlation between plasma FVIII levels, coagulant activity, and clinical manifestations.

Treatment regimens are typically either on-demand therapy (given when a bleeding occurs) or prophylaxis (which consists of regular infusion of FVIII given at scheduled intervals (e.g., 2x per week, 3x per week) to prevent bleeding).

Standard prophylaxis using regularly scheduled infusions at doses and dose intervals sufficient to prevent bleeding events have been demonstrated to result in not only preservation of joint function and reducing the incidence of early disability and death, but also reduced frequency of intracranial hemorrhage, fewer hospital admissions, less joint surgery, and fewer missed days at work.[2, 6] These benefits are the direct result of continuously improving standard of care, earlier diagnosis, and start of prophylactic treatment, and was made possible by the greater availability of a safe and consistently available source of factor concentrates.

However, due to the diverse access to hemophilia treatment centers in different cities in China, the treatment approach mostly used for hemophilia A patients is on-demand treatment, especially for adult patients. Historically, lack of access to routine prophylaxis treatment in some Chinese regions increased the likelihood of joint damage and compromised health-related quality of life. Low dose secondary prophylaxis (10 IU/kg, 2 times per week, 10-30 IU/kg weekly) has been explored as a cost saving approach for the treatment of Chinese patients with hemophilia.[7, 8] Although the results of this approach have been encouraging, there remains the goal of establishing effective individualized prophylaxis and standardized care for Chinese hemophilia patients. In recent years, the proportion of prophylaxis use in pediatric patients is increasing.[3]

2.3 Benefit/Risk Assessment

The benefit/risk assessment of KOVALTRY has been demonstrated as favorable in the LEOPOLD program for children, adolescents, and adults.

In general, in clinical trials of both children and adolescents/adults, KOVALTRY has been shown to be well tolerated.

The most significant risk with KOVALTRY, like any FVIII replacement product, is the development of FVIII inhibitors. Detailed information about the known and expected benefits and risks and expected adverse events of KOVALTRY may be found in the Chinese Package Insert (see Section 12).

2.3.1 Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/ Rationale for Risk	Mitigation Strategy
Important identified risks: • Development of factor VIII inhibitors • Hypersensitivity and allergic reactions	Development of factor VIII inhibitors: The formation of neutralizing antibodies (inhibitors) to FVIII is a known complication in the management of individuals with hemophilia A and a class effect for all FVIII products. For previously untreated patients (PUPs), the risk to develop inhibitors is considered very common (approximately 30% to 50%), whereas the risk for PTPs is considered uncommon (<1%). Hypersensitivity and allergic reactions: Hypersensitivity reactions, including anaphylaxis, are possible with KOVALTRY. No anaphylactic reactions have been reported with KOVALTRY. Allergic type hypersensitivity reactions are possible with KOVALTRY. The product may contain traces of hamster or mouse proteins, which in some patients may cause allergic reactions.	The informed consent will outline the important identified and potential risks. Inhibitor titer is assessed at scheduled study visits. Planned time points for all safety assessments are provided in the Schedule of Activities [Section 1.3].
Study Intervention - KOVALTRY		
Drug infusion: This procedure can cause pain or bruising at the site of the infusion.	The study treatment is administered as intravenous infusion [see Section 6.1].	Study participants will be informed of these potential risks in the informed consent.
Study Procedures		
Blood draw: This procedure can cause discomfort from the needle, pain, and bruising at the site of the draw. There is rarely any infection. Drug infusion: This procedure can cause pain or bruising at the site of the infusion.	Blood samples will be obtained at baseline to confirm study eligibility. As outlined in Section 7.1 and Section 7.2, there will be additional blood draws at scheduled study visits for FVIII recovery, FVIII inhibitor assessment, and for a subset of participants in Part A, additional PK analysis sampling.	Study participants will be informed of these potential risks in the informed consent.

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. KOVALTRY is a full-length rFVIII product approved for the prevention and treatment of bleeding episodes in patients with hemophilia A.[1] The LEOPOLD clinical trial program conclusively demonstrated that KOVALTRY is efficacious in preventing and treating bleeding episodes as well as maintaining hemostasis during surgery in children, adolescents, and adults with severe hemophilia A.[9, 10, 11]

Prophylaxis with KOVALTRY decreases bleeding frequency compared with on-demand treatment. KOVALTRY prophylaxis is efficacious when administered either twice weekly or three times weekly, and in addition in pediatric patients also every other day.[9, 10, 11] LEOPOLD study data support the use of individualized prophylaxis dosing of KOVALTRY based on a patient's clinical history. In the LEOPOLD clinical studies, a low pre-study bleeding rate was a good predictor of a low annualized bleeding rate with KOVALTRY prophylaxis.[9] KOVALTRY also effectively maintains hemostasis in patients with hemophilia A undergoing major or minor surgical procedures.[9, 10, 11]

The risk associated with infusion of study treatment is not more than what would be expected for hemophilia A patients receiving KOVALTRY as standard of care.

Blood samples will be collected at screening to confirm study eligibility, during scheduled study visits as part of safety assessment for the study, and for the PK sub-study (optional for children <12 years of age) in Part A. 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 KOVALTRY 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. Additionally, the protocol includes a guideline providing the recommended blood volume to be drawn from children 1-10 kg for study related tests. Therefore, it is expected that the risk associated with blood draws is not more than would be expected with standard of care.

2.3.3 Overall Benefit: Risk Conclusion

Considering the measures taken to minimize risk to participants in this study, the potential risks identified in association with KOVALTRY are justified by the anticipated benefits of prophylaxis treatment with KOVALTRY for study participants.

3. Objectives and Endpoints

3.1 Objectives and Endpoints - Part A (PTPs)

Objectives	Endpoints
Primary	
Efficacy	
• Evaluate the efficacy of prophylaxis treatment with KOVALTRY in Chinese children (<12 years) and adolescents/adults (≥12 years) with severe hemophilia A	• Annualized bleeding rate (ABR)
Secondary	
Efficacy	
• Evaluate efficacy of KOVALTRY for treatment of bleeding episodes • Assess efficacy within 48 hours of previous prophylaxis infusion • Evaluate the in vivo recovery of KOVALTRY • Hemostatic control for minor surgeries	• Number of infusions needed to achieve hemostasis and response to treatment of bleeds • ABR within 48h of previous prophylaxis infusion • In vivo recovery of KOVALTRY at baseline, 2 months after start of study treatment, and study end • Physician assessment of adequacy of hemostasis in minor surgery
Safety	
• Assess the safety of KOVALTRY for prophylaxis and treatment of bleeding episodes in Chinese children (<12 years) and adolescents/adults (≥12 years) with severe hemophilia A	• FVIII inhibitor development by the Nijmegen Bethesda assay • Treatment-emergent adverse events (TEAEs)
Pharmacokinetics	
• Evaluate pharmacokinetics (PK) of KOVALTRY in Chinese children (<12 years) and adolescents/adults (≥12 years to 65 years) severe hemophilia A patients	• PK parameters include C_{max}, AUC, and $t_{½}$

3.2 Objectives and Endpoints - Part B (PUPs/MTPs)

Objectives	Endpoints
Primary	
Efficacy	
• Assess the efficacy of KOVALTRY within 48 hours of previous prophylaxis infusion in previously untreated/minimally treated Chinese children (<6 years of age) with severe hemophilia A	• ABR within 48 hours of previous prophylaxis infusion
Secondary	
Efficacy	
• Evaluate the efficacy of prophylaxis treatment with KOVALTRY • Assess the efficacy of KOVALTRY for treatment of bleeding episodes • Evaluate the in vivo recovery of KOVALTRY • Hemostatic control for minor surgeries	• ABR during the prophylaxis period • Number of infusions required to treat a bleed and response to treatment of bleeds • In vivo recovery of KOVALTRY at baseline and study end • Physician assessment of adequacy of hemostasis in minor surgery
Safety	
• Assess the safety of KOVALTRY for prophylaxis and treatment of bleeding episodes in previously untreated/minimally treated Chinese children (<6 years of age) with severe hemophilia A	• FVIII inhibitor development by the Nijmegen Bethesda assay • Treatment-emergent adverse events (TEAEs)

4. Study Design

4.1 Overall Design

This is a multicenter, uncontrolled, open-label, single arm treatment, 2-part study in previously treated, previously untreated, and minimally treated Chinese children and adolescents/adults with severe hemophilia A.

Study participants who develop high-titer inhibitor (>5 BU/mL, confirmed by central lab for Part A or local laboratory for part B) related to study drug, that interferes with effective treatment with FVIII, may opt to enter optional ITI treatment with study drug (Section 10.5.1) or leave the study and be treated with other therapies outside of the study at the discretion of the investigator. The optional ITI treatment with the study drug within the study requires a separate signed informed consent. Refer to Section 10.5 for additional details.

4.1.1 Part A (PTPs)

Part A will assess the efficacy, safety, and PK of KOVALTRY in previously treated Chinese children and adolescents/adults with severe hemophilia A. Part A is planned to investigate a total of 42 PTPs. Efficacy and safety assessments are outlined in the Schedule of Activities (SoA) in Section 1.3.1.

PK will be assessed in a subset of 12 children (<12 years) and 12 adolescents/adults (≥12 years). Details of the PK parameters to be assessed are provided in Section 8.6.

Efficacy and safety data for use of KOVALTRY for treatment of bleeding episodes will also be collected.

- Study participants will be treated for 6 months at the following doses according to the prescribing information for KOVALTRY:
  - Study participants ≤12 years of age: 25 to 50 IU of KOVALTRY per kg body weight twice weekly, three times weekly, or every other day according to individual requirements for 6 months
  - Study participants >12 years: 20 to 40 IU of KOVALTRY per kg of body weight two or three times per week according to individual requirements for 6 months
- Part A will include 5 study visits (Screening, Baseline, Visit 3/Month 1, Visit 4/Month 2, Visit 5/Final visit/Early Termination). All participants will also receive a safety follow-up call approximately 2 weeks after the final study visit.

4.1.2 Part B (PUPs/MTPs)

Part B will assess the efficacy and safety of KOVALTRY in previously untreated/minimally treated Chinese children with severe hemophilia A. Part B will investigate approximately 6 PUPs/MTPs. Efficacy and safety assessments are outlined in the SoA in Section 1.3.2.

Efficacy and safety data for the use of KOVALTRY for treatment of bleeding episodes will also be collected.

- Study participants will be treated until at least 50 ED is achieved.
  - Treatment may begin with start of prophylaxis with 15 to 50 IU/kg (minimum dose: 250 IU) at least 1 day a week; alternatively, prophylaxis

can be started directly with a once-a-week schedule minimum dose of 250 IU for PUPs/MTPs of any weight.

- The starting dose may be tailored to the participant's weight or demonstrated bleeding tendency.
- Individual participant dose decisions are at the discretion of the investigator.

- Part B will include 8 study visits (Screening, Baseline, Visit 3 [approximately 5 ED], Visit 4 [approximately 10 ED], Visit 5 [approximately 15 ED], Visit 6 [approximately 20 ED], Visit 7/Interim visit [approximately 30 to 40 ED], and Visit 8/Final visit [50 ED]/Early Termination). All parents/caregivers of participants in Part B will receive a safety follow-up call approximately 2 weeks after the end of treatment.

4.2 Scientific Rationale for Study Design

Part A of this study will collect clinical data in 42 previously treated Chinese participants with severe hemophilia A (30 children and 12 adolescents/adults) to provide additional efficacy and safety data for the use of KOVALTRY for prophylaxis and treatment of bleeding episodes in this patient population. Pharmacokinetic data will also be collected from 24 participants (see Section 8.6 for details).

Part B of this study will collect clinical data in approximately 6 previously untreated/minimally treated Chinese participants with severe hemophilia A (6 children) to provide additional efficacy and safety data for the use of KOVALTRY for prophylaxis and treatment of bleeding episodes in this patient population.

4.2.1 Participant Input into Design

Not applicable.

4.3 Justification for Dose

The routine prophylaxis doses used in this study are the approved doses in the Chinese prescribing information for KOVALTRY (Section 12).

4.3.1 Routine Prophylaxis

- Adults and adolescents: 20 to 40 IU of KOVALTRY per kg of body weight two or three times per week
- Children ≤12 years old: 25 to 50 IU of KOVALTRY per kg body weight twice weekly, three times weekly, or every other day according to individual requirements

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

4.3.1.1 Prophylaxis Treatment for Adolescent and Adult Patients

For long-term prophylaxis against bleeding in patients with severe hemophilia A, the recommended doses are 20 to 40 IU of factor VIII per kg body weight two or three times per week. In some cases, especially in younger patients, shorter dosage intervals or higher doses may be used.

4.3.1.2 Pediatric Patients

KOVALTRY is approved for use in pediatric patients. Safety and efficacy studies have been performed in children 0-12 years. The recommended prophylaxis doses are 25-50 IU/kg twice weekly, three times weekly, or every other day according to individual requirements. For pediatric patients above the age of 12, the dose recommendations are the same as for adults.

For PUPs/MTPs, prophylaxis with study intervention may be initiated at 15 to 50 IU/kg (minimum dose: 250 IU) at least 1 day per week.

Frequent infusions may be difficult for small children and their caregivers. Consequently, the benefit for each individual child must be evaluated against this burden, particularly in very young children for whom venous access may be difficult.

4.3.2 Treatment of Bleeding Episodes

The required dose is determined using the following formula:

Required units = body weight (kg) x desired factor VIII rise (% or IU/dL) x reciprocal of observed recovery

The usual single dose for bleeding episodes of mild to moderate severity is 10-30 IU/kg body weight. Higher dosages are recommended for life threatening or major hemorrhages.

For participants with a recovery below 2 (which may occur, e.g., in small children), higher dosages may be needed. Further guidance is included in Section 12.

4.4 End of Study Definition

A participant is considered to have completed the study if he has completed the last study visit, as shown in the Schedule of Activities for Part A (Section 1.3.1) or Part B (Section 1.3.2), or optional ITI treatment (Section 10.5.2).

Completion of Part A is when the last participant in Part A completes the final visit or early termination as shown in the Schedule of Activities for Part A (Section 1.3.1).

Completion of Part B is when the last participant in Part B completes the final visit or early termination as shown in the Schedule of Activities for Part B (Section 1.3.2).

Study participants who develop high-titer FVIII inhibitor and decide to enter optional ITI treatment with study intervention will discontinue participation in either Part A or Part B and complete the Early Termination visit. The end of study for these participants is defined as completion of the Optional ITI Treatment (Section 10.5.1).

Study participants who develop high titer FVIII inhibitor and decide to receive ITI with another product outside of the study will complete the Early Termination visit and leave the study.

The study itself will be considered complete after the last visit of the last participant for all centers has occurred.

5. Study Population

Part A of the study plans to enroll 42 previously treated severe hemophilia A, defined as less than 1% of factor VIII in the blood (based on one-stage assay), patients (PTPs) in China. Approximately 30 children aged <12 years and 12 adolescents/adults ≥12 years up to 65 years with documented severe hemophilia A will be enrolled in two age groups.

Part B of the study plans to enroll approximately 6 Chinese PUPs/MTPs (children <6 years) with documented severe hemophilia A, defined as less than 1% of factor VIII in the blood (based on one-stage assay).

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

5.1 Inclusion Criteria

5.1.1 Part A (PTPs) Inclusion Criteria

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

Age

1. Participants enrolled as children must be <12 years at the time of their parent or legal representative's signature of informed consent on the participant's behalf, or if enrolled as adolescents/adults, must be ≥ age 12 to 65 years at the time of signed informed consent.

Type of Participant and Disease Characteristics

2. Chinese participants with severe hemophilia A (defined as FVIII:C <1% with one-stage clotting assay documented at the time of screening). If screening results show FVIII:C as equal to or higher than 1%, then severe hemophilia A may be confirmed by documented historical evidence from a (certified) clinical laboratory demonstrating <1% FVIII:C as determined by a one-stage clotting assay.
3. Currently receiving on-demand or any type of prophylaxis treatment regimen with any FVIII product (excluding treatment with fresh-frozen plasma and cryo-precipitate).
4. For participants <12 years of age, ≥50 exposure days (ED); for participants ≥12 to 65 years of age, ≥150 ED with any Factor VIII product (excluding treatment with fresh-frozen plasma and cryo-precipitate).
5. No current evidence of inhibitor antibody as measured by the Nijmegen-modified Bethesda assay [<0.6 Bethesda units (BU)/mL] in 2 consecutive samples and absence of clinical signs or symptoms of decreased response to FVIII administration. (First negative sample can be historical if obtained within 3 months prior to screening with a result of <0.6 BU/mL by classical Bethesda assay. The testing for a second negative, confirmatory sample must, in all cases, be performed by a central laboratory using the Nijmegen-modified Bethesda test. If a first recent sample is not available, then testing for 2 negative samples must be performed by the central laboratory at least 1 week apart). Participants may not receive FVIII within 72 hours prior to the collection of samples for inhibitor testing.

6. No history of FVIII inhibitor formation. Documentation of negative result in medical records is required (Nijmegen-modified Bethesda assay or classical Bethesda assay); 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 successive negative results (<0.6 BU/mL) thereafter are eligible.

Sex

7. Male participants only.

Informed Consent

8. Each adult participant must be capable of giving signed informed consent/assent as described in Section 10.1.2, which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol. For children and adolescents under the age of consent/assent in China, parents or a legal representative must be able to provide a signed informed consent/assent on behalf of the minor child/adolescent.

Other

9. Willingness and ability of participants, parents, or caregiver to comply with prophylaxis schedule and complete training on the use of the study electronic patient diary (EPD) and to use the diary to document bleeding and infusion information during the study.

5.1.2 Part B (PUPs/MTPs) Inclusion Criteria

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

Age

1. Participants must be <6 years of age at the time of their parent or legal representative's signature of informed consent on the participant's behalf.

Type of Participant and Disease Characteristics

2. Chinese participants with severe hemophilia A (defined as FVIII:C <1% with one-stage clotting assay documented at the time of screening). If screening results show FVIII:C as equal to or higher than 1%, then severe hemophilia A may be confirmed by documented historical evidence from a (certified) clinical laboratory demonstrating FVIII:C <1% as determined by a one-stage clotting assay.
3. PUPs must have no previous exposure to any FVIII product.

   MTPs must have no more than 1 ED with any purified FVIII concentrate or 3 exposures with FFP or cryoprecipitate.
4. MTPs have no current evidence of inhibitor antibody as measured by the Nijmegen-modified Bethesda assay (<0.6 BU/mL) in 2 consecutive samples and must have absence of clinical signs or symptoms of decreased response to FVIII administration. Testing for the 2 negative samples must be performed by the local laboratory at least 1 week but not more than 2 weeks apart. Participants may not receive FVIII product within 72 hours prior to the collection of samples for inhibitor testing.

5. PUPs and MTPs must observe a 6-month washout period if they have received subcutaneous factor substitution therapy (emicizumab).
6. PUPs may be included if they will receive their first FVIII dose with KOVALTRY for treatment of first bleeds and agree to start prophylaxis as part of their care.

   MTPs may be included if they agree to start prophylaxis as part of their care.

Sex

7. Male participants only

Informed Consent

8. The parents or a legal representative of the participant must be able to provide a signed informed consent on behalf of the participant.

Other

9. The participant's parent/caregiver must be willing and able to comply with the prophylaxis schedule and to complete training on the use of the study EPD and use the EPD to document bleeding and treatment information during the study.

5.2 Exclusion Criteria

5.2.1 Part A (PTPs) Exclusion Criteria

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

Medical Conditions

1. Any other bleeding disease that is different from hemophilia A (e.g., von Willebrand disease, hemophilia B).
2. Platelet count <100 000/mm^3 based on screening laboratory assessments.
3. Impaired renal function (serum creatinine >2.0 mg/dL) or active liver disease (alanine aminotransferase/aspartate aminotransferase [ALT/AST] >5x ULN) based on screening laboratory.
4. Human immunodeficiency virus (HIV) positive with an absolute CD4 lymphocyte cell count <250 cells/μL.
5. Known hypersensitivity to the active substance, mouse or hamster protein.

Prior/Concomitant Therapy

6. Receiving chemotherapy or immune modulatory drugs (e.g., intravenous [IV] immunoglobulin, cyclosporine) other than anti-retroviral chemotherapy or chronic use of oral or intravenous (IV) corticosteroids (>14 days) within the last 3 months. Brief courses of prednisone/methyprednisolone (<14 days) for treatment of disorders such as synovitis, asthma, etc. are allowed at the discretion of the treating physician
7. Requiring any pre-medication to tolerate FVIII infusions (e.g., antihistamines).

Prior/Concurrent Clinical Study Experience

8. Currently participating in another investigational drug study, or having previously participated in a clinical study involving an investigational drug within 30 days of signing informed consent or participated in completed interventional clinical studies with BAY 81-8973 (KOVALTRY).

Other Exclusions

9. Unwilling to comply with study visits or other protocol requirements or is not suitable for participation in this study for any reason, according to the Investigator.
10. Planned major surgery, defined as surgery with respiratory assistance and/or general anesthesia.
11. Close affiliation with the investigational site; e.g., a close relative of the investigator, dependent person (e.g., employee or student of the investigational site).

5.2.2 Part B (PUPs/MTPs) Exclusion Criteria

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

Medical Conditions

1. Any other bleeding disorder that is different from hemophilia A (e.g., von Willebrand disease, hemophilia B).
2. Platelet count <100 000/mm^3 based on screening laboratory assessments.
3. Impaired renal function (serum creatinine >2× upper limit of normal [ULN]) or active liver disease (alanine aminotransferase [ALT] or aspartate aminotransferase [AST] >5× ULN) based on screening laboratory assessments.
4. MTPs with history of FVIII inhibitor formation.
5. Known hypersensitivity to the active substance, mouse or hamster protein.
6. First treatment with KOVALTRY for high-risk bleeding situations (e.g., surgery, intracranial bleed) or requiring intensive or prolonged treatment.
7. Planned major surgery, defined as surgery with respiratory assistance and/or general anesthesia.

Prior/Concomitant Therapy

8. Receiving chemotherapy or immune modulatory drugs (e.g., IV immunoglobulin, cyclosporine) other than anti-retroviral chemotherapy or chronic use (>14 days) of oral or IV corticosteroids within the last 3 months. Brief courses (<14 days) of prednisone/methyprednisolone for treatment of disorders such as synovitis, asthma, etc. are allowed at the discretion of the treating physician.
9. Requiring any pre-medication to tolerate FVIII infusions (e.g., antihistamines).

Prior/Concurrent Clinical Study Experience

10. Currently participating, or have participated within 30 days of signing informed consent, in another clinical study involving an investigational drug.

Other Exclusions

11. Unwilling to comply with study visits or other protocol requirements or is not suitable for participation in this study for any reason, according to the investigator’s judgment.
12. Close affiliation with the investigational site (e.g., a close relative of the investigator, dependent person [e.g., employee or student of the investigational site]).
13. Unable to tolerate volume of blood draws required for study participation (see Section 10.2).

5.3 Lifestyle Considerations

No restrictions are required.

5.3.1 Meals and Dietary Restrictions

No restrictions are required.

5.3.2 Caffeine, Alcohol, and Tobacco

No restrictions are required.

5.3.3 Concomitant Medications

Medications that cause a bleeding diathesis (for example, Aspirin® or any acetylsalicylic acid) should be avoided in individuals with hemophilia, except as specifically prescribed by a treating physician. Low dose aspirin should not be discontinued in participants who have been identified to be at risk for cardiovascular events. Further details are provided in Section 6.5.

5.4 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently receiving study intervention. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse events (AEs).

Individuals who do not meet the criteria for participation in this study (screen failure) cannot be rescreened.

6. Study Intervention

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

6.1 Study Intervention Administered

All treatment decisions for identifying appropriate prophylactic treatment regimen should be guided by clinical judgment based on the approved prescribing information (PI) and the individual participant characteristics and treatment response.

Table 6–1: Study Intervention by Arm and Dose

	Part A		Part B
Arm Name	**Child (Age <12 years)**	**Adolescent/Adult (Ages ≥12 to 65 years)**	**Child (Age <6 years)**
Intervention Name	KOVALTRY	KOVALTRY	KOVALTRY
Type	Full-length human recombinant Factor VIII (rFVIII) protein	Full-length human recombinant Factor VIII (rFVIII) protein	Full-length human recombinant Factor VIII (rFVIII) protein
Dose Formulation	Powder for solution for infusion or infusion	Powder for solution for infusion or infusion	Powder for solution for infusion or infusion
Unit Dose Strengths	250 IU, 500 IU, 1000 IU	250 IU, 500 IU, 1000 IU	250 IU, 500 IU, 1000 IU
Dosage (for prophylaxis)	25 to 50 IU of KOVALTRY per kg body weight (rounded to the nearest vial size) twice weekly, three times weekly, or every other day according to individual requirements for 6 months	12 year-old: 25 to 50 IU of KOVALTRY per kg body weight (rounded to the nearest vial size) twice weekly, three times weekly, or every other day for 6 months >12 year-old: 20 to 40 IU of KOVALTRY per kg of body weight (rounded to the nearest vial size) two or three times per week for 6 months	15 to 50 IU (minimum 250 IU) of KOVALTRY per kg body weight [rounded to the nearest vial size]) at least 1 day per week. Alternatively, prophylaxis can be started directly with a once-a-week schedule minimum dose of 250 IU for PUPs/MTPs of any weight. The starting dose may be tailored to the participant's weight or demonstrated bleeding tendency. Treatment is continued until 50 ED is achieved.
Route of Administration	IV infusion	IV infusion	IV infusion

	Part A		Part B
Arm Name	**Child (Age <12 years)**	**Adolescent/Adult (Ages ≥12 to 65 years)**	**Child (Age <6 years)**
Packaging and Labeling (identical for all arms)	Study intervention will be provided in vials packaged together with a container of the appropriate amount of sterile water for infusion for reconstitution. For KOVALTRY, the volume of diluent is 2.5 mL for all vial sizes. The vials will also be supplied with an infusion set composed of 1 syringe containing the diluent and 1 butterfly needle to facilitate infusion. Instructions for reconstitution are supplied in each kit. The kits will be labeled as required by the Chinese Regulatory Authority. Instructions on storage and transport of the drugs provided for home administration will be provided in training given at the Baseline visit.	Study intervention will be provided in vials packaged together with a container of the appropriate amount of sterile water for infusion for reconstitution. For KOVALTRY, the volume of diluent is 2.5 mL for all vial sizes. The vials will also be supplied with an infusion set composed of 1 syringe containing the diluent and 1 butterfly needle to facilitate infusion. Instructions for reconstitution are supplied in each kit. The kits will be labeled as required by the Chinese Regulatory Authority. Instructions on storage and transport of the drugs provided for home administration will be provided in training given at the Baseline visit.	Study intervention will be provided in vials packaged together with a container of the appropriate amount of sterile water for infusion for reconstitution. For KOVALTRY, the volume of diluent is 2.5 mL for all vial sizes. The vials will also be supplied with an infusion set composed of 1 syringe containing the diluent and 1 butterfly needle to facilitate infusion. Instructions for reconstitution are supplied in each kit. The kits will be labeled as required by the Chinese Regulatory Authority. Instructions on storage and transport of the drugs provided for home administration will be provided in training given at the Baseline visit.
Current/Former Name(s) or Alias(es)	Commercial name: KOVALTRY (BAY 81-8973)	Commercial name: KOVALTRY (BAY 81-8973)	Commercial name: KOVALTRY (BAY 81-8973)

KOVALTRY will also be used for treatment of bleeding events and with surgical procedures (see Section 10.4) and optional ITI (see Section 10.5).

For optional ITI treatment with Kovaltry, ITI will be provided at a dose of up to 200 IU/kg daily for up to a maximum of 18 months or until failure (see Section 10.5 for additional information).

6.2 Preparation/Handling/Storage/Accountability

The instructions for reconstitution using a vial adaptor will be provided to the participant and/or his parent/caregiver at the start of the study, and study site staff will instruct all participants and/or their caregivers on how to reconstitute and administer KOVALTRY.

The participants and/or their caregivers will be instructed to administer reconstituted KOVALTRY as soon as possible, and no longer than 3 hours after reconstitution, according to the individual participant's dosing schedule.

KOVALTRY must be stored under refrigeration (2°C to 8°C, do not freeze). Participants and parents/caregivers will be provided with detailed instructions for proper storage of the study intervention.

KOVALTRY must be stored at the investigational site in accordance with Good Clinical Practice (GCP) and Good Manufacturing Practice (GMP) requirements and the instructions given by the clinical supplies department of the Sponsor or its affiliates.

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

1. The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study intervention received, and any discrepancies are reported and resolved before use of the study intervention.
2. Only participants enrolled in the study will receive study intervention and only authorized site staff 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. Participants and/or their parents/caregivers will be instructed on proper storage at home.
3. The personnel will use the study intervention only within the framework of this clinical study and in accordance with this protocol.
4. The authorized site staff is responsible for study accountability, reconciliation, and record maintenance. Receipt, distribution, return and destruction (if any) of the study intervention must be properly documented according to the Sponsor's agreed and specified procedures.
5. Further guidance and information for the final disposition of unused study interventions are provided separately.

6.3 Measures to Minimize Bias: Randomization and Blinding

Not applicable. The study arms are based only on age and/or treatment status (PTPs and PUPs/MTPs). This is an open label study, and no blinding or randomization will be used.

6.4 Study Intervention Compliance

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

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

When participants are dosed at the site (at Baseline and the indicated study visits in Section 1.3.1 [Part A] or Section 1.3.2 [Part B] as per their individual participant's regimen), they will receive study medication according to the standard of the institution. The date and time of each dose administered in the clinic will be recorded in the source documents and recorded in the case report form (CRF).

The majority of dosing will be done at home, by the participant or his parent/caregiver, in accordance with the written instructions and demonstration provided by study center staff at the Baseline visit. Instruction on reconstituting KOVALTRY and other aspects of IV administration will be provided in detail.

In Part A, KOVALTRY will be dispensed on a monthly basis (in accordance with the individual drug dispensing schedule every 28 [±7] days) at the study center and will not be linked to the scheduled study visit schedule (see Section 1.3.1). In Part B, drug dispensing will be done in accordance with the individual drug dispensing schedule; additional drug dispensing visits might be performed between Visit 6 and the Final visit in order to ensure study participants have sufficient study drug to cover the period between the scheduled study visits (see Section 1.3.2).

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

The EPD will be reviewed at visits and at regular contacts with the participant and/or his parent/caregiver during the study.

6.5 Concomitant Therapy

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

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

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

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

All medications and blood products required by the participant after the informed consent is signed, including FVIII products other than study intervention, will be listed in the appropriate eCRF page. All concurrent prescription and non-prescription medications including over-the-counter and alternative preparations (including herbal remedies, vitamins, and health food supplements), antibiotics, and pain medications being administered starting at least 3 months, and FVIII and bispecific activated FVIII mimetic products at least 12 months prior to study enrollment, will be recorded in the CRF at screening and throughout the treatment period and follow-up call.

The participant should not be taking any other investigational drug or any other FVIII treatment (except in emergencies) while receiving treatment with KOVALTRY. Pre-medications to tolerate treatment with KOVALTRY are not allowed. Use of topical anesthetics prior to venipuncture is permitted.

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

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

6.5.1 Rescue Medicine

Not applicable.

6.6 Dose Modification

6.6.1 Dose Modification in Part A (PTPs)

Dosing recommendations for prophylaxis in adults/adolescents and children are provided as per the approved label. Dose modifications should be individualized based on clinical response at the investigator discretion.

Study participants receiving prophylaxis treatment 2x per week (i.e., on a 2x/week prophylaxis regimen) should increase prophylaxis dosing frequency to three times per week if they experience 2 or more spontaneous joint and/or muscle bleeding episodes within a 6-week period.

Study participants receiving prophylaxis treatment 3x per week (i.e., on a 3x/week prophylaxis regimen) should increase prophylaxis dosing frequency to every other day if they experience 2 or more spontaneous joint and/or muscle bleeding episodes within a 6-week period.

6.6.2 Dose Modification in Part B (PUPs/MTPs)

Individual participant dose decisions are at the discretion of the investigator.

Recent studies have demonstrated that the timing of the first exposures to FVIII may be critical for the tolerance of the drug. The CANAL study showed that early intensive treatment, such as those required for surgery or severe bleeds, increased the risk for inhibitor development, whereas regular prophylaxis was associated with a lower risk.[12] This observation was subsequently supported by studies demonstrating lower inhibitor rates in boys treated with low dose early prophylaxis in treatment centers in Germany.[13]

Taking these observations into account, the following are treatment recommendations for PUPs/MTPs participating in Part B:

1. Prophylaxis can be started directly with 15 to 50 IU/kg (minimum dose: 250 IU) once per week; the starting dose may be tailored to the participant's weight or demonstrated bleeding tendency.
2. Alternatively, treatment can be initiated with an on-demand regimen. Prophylaxis should begin after a minimal number of on-demand FVIII exposures with KOVALTRY (no more than 2 to 3 bleeding events) or when the child is large enough to tolerate weekly infusion.
3. Avoid starting prophylaxis during a febrile illness or other identified inflammatory events.
4. Avoid surgery or need for high dose intensive treatment lasting more than 4 days during the first 20 ED.

5. KOVALTRY must not be given as prophylaxis for vaccinations.

After treatment with KOVALTRY begins, inhibitor testing every 3 to 5 ED is required until 20 ED are accumulated or in case of non-response to treatment.

6.6.3 Breakthrough Bleeds and Minor Surgery

KOVALTRY will also be used for the treatment of bleeding episodes in this study. The dose should be individualized according to severity of the specific bleeding episode.

KOVALTRY will also be used for perioperative management of minor surgery that may occur during the course of the study.

The dosages used for treatment of breakthrough bleeds or minor surgery will be at the discretion of the investigator.

A guide for dosing for bleeding episodes and surgery, as well as a guide for the assessment of adequacy of hemostasis during surgery, are provided in Section 10.4.

Definitions of response to treatment of breakthrough bleeds (i.e., excellent, good, moderate, or poor [or none]) is provided in Section 7.3.1.

6.7 Intervention After the End of the Study

No intervention or extended treatment will be provided after the end of the study.

6.8 Discontinuation of Study Intervention and Participant Discontinuation/Withdrawal

6.8.1 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, but will be evaluated for safety at his last study visit. Unscheduled visits are permitted at any time at the discretion of the investigator.

See the SoAs (Section 1.3.1 for Part A and Section 1.3.2 for Part B) for data to be collected at the time of intervention discontinuation and for any further evaluations that need to be completed. For cases of early termination in Part A, all investigations for Visit 5 should be performed. For cases of early termination in Part B, all investigations for Visit 8/Final visit should be performed.

6.8.2 Temporary Discontinuation of Study Intervention

Participants who have an emergency major surgery during the study may be treated with KOVALTRY or other FVIII, according to local practice at the discretion of investigators. Participants will resume their treatment assignment of KOVALTRY as per this protocol after surgical recovery. Duration of interruption of study intervention (i.e., prophylaxis treatment with KOVALTRY) should not be more than 2 weeks.

During the trial, it is expected that all reasonable attempts will be made to ensure that study participants will comply with and adhere to their prophylaxis infusion schedule with few interruptions. In rare instances, it may be necessary for a study participant to temporarily discontinue study intervention (e.g., difficulty with IV access in children, travel to locations where appropriate support for infusions is not available). Study participants/caregivers should inform the investigator of all such situations, and the reasons must be documented in the

medical record. Prolonged periods (>2 weeks) or repeated breaks in the prophylaxis schedule should be avoided and could result in the study participant being removed from the study.

6.8.3 Participant Discontinuation/Withdrawal from the Study

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

A participant may be withdrawn from the study at any time:

- At their own request or at the request of their parent/legal representative. Without giving reasons, a participant may decline to participate further.
- At the discretion of the investigator for safety, behavioral, compliance, or administrative reasons.

A participant must be withdrawn from the study:

- In case of positive inhibitor result at Screening or in case of high titer inhibitor result at the Baseline visit.
- In case of development of a high-titer inhibitor related to the study drug (>5 BU/mL, confirmed on a second measurement done in central laboratory [Part A] or in local laboratory [Part B] within 2 weeks of notification of initial detection of high-titer inhibitor) that interferes with effective treatment with FVIII and the investigator believes that it is in the best interest of the participant to receive treatment for management with ITI outside of the study. There is the option to receive ITI with study drug. In this case, the participant discontinues participation in Part A or Part B and continues in the Optional ITI Treatment. ITI with study drug will be provided at a dose of up to 200 IU/kg daily for up to a maximum of 18 months (see Section 10.5.1 for additional information). While awaiting confirmatory testing for the initial result, treatment will be at the investigator's discretion according to local standard of care.
- If he fails to comply with scheduled appointments for the study-related evaluations and with EPD data entry to an extent that compromises collection of critical data.

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

At the time of discontinuing from the study, any attempts should be taken to conduct an early discontinuation visit (Visit 5 for Part A or Visit 8/Final visit for Part B). See the SoAs (Section 1.3.1 for Part A and Section 1.3.2 for Part B) 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 reason for each withdrawal must be recorded in the CRF and in participant´s medical record.

6.9 Lost to Follow-Up

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

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

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a 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 will be considered lost to follow-up.

7. Study Assessments and Procedures

The list of study assessments and timing of these assessments and procedures are displayed in the SoAs (Section 1.3.1 for Part A and Section 1.3.2 for Part B) and are described in detail here.

General Study Procedure Notes:

- Protocol waivers or exemptions are not allowed.
- Immediate safety concerns should be discussed with the Sponsor as soon as possible after the investigator becomes aware of an occurrence to determine if the participant should continue or discontinue study intervention.
- Adherence to the study design requirements, including those specified in the SoAs (Section 1.3.1 for Part A and Section 1.3.2 for Part B), 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 time frame defined in the SoA.

If deemed necessary for an individual participant, the investigator or designee, at his/her discretion, may arrange visits in addition to the scheduled study visits. Unscheduled visits will be documented in the eCRF.

Visits during Optional ITI Treatment are described in Section 10.5.2.

Blood Draw Volume

Every effort has been made to minimize the volumes of blood required for participation in the study. 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 (see Section 10.2). For participants <10 kg, the maximum amount of blood collected from each participant over the duration of the study, including any extra assessments that may be required, should follow recommendations for blood draws in participants <10 kg. Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

7.1 Study Visits - Part A (PTPs)

7.1.1 Screening/Visit 1 (Up to 6 Weeks Prior to Baseline)

After obtaining signed Informed Consent from the prospective participant or his parent or legal representative, as required, the following screening assessments will be obtained (screening assessments may require multiple site visits prior to baseline):

- Inclusion/exclusion criteria verification
- Allocation of a unique participant number
- Review of eligibility requirements; no participant should receive study intervention unless all inclusion and exclusion criteria are met as listed in

Section 5.1 and Section 5.2. Confirmation of selection criteria may be based on medical records for some conditions, but laboratory test results must be available for the listed items to confirm eligibility.

- Collect demographic data (e.g., age, sex [male only], race, etc.)
- Height and body weight (kg)
- Obtain a complete medical and surgical history (e.g., general, hemophilia, family history of hemophilia, and history of inhibitor development)
    - Specific information on history of hemophilia (date of diagnosis, start of therapy, prior and current factor VIII products, number of ED, family history, FVIII level at diagnosis, family and personal history of past inhibitor formation, current treatment product and regimen, number and type of bleeding episodes in the last 12 months, and presence and location of target joints [defined as at least 3 spontaneous bleeding episodes into a single joint within a consecutive 6-month period])
- Prior medication (medication history), see Section 6.5
- Concomitant medication, see Section 6.5
- Physical examination, see Section 8.1
- Vital signs (including systolic and diastolic blood pressure, heart rate, and body temperature), see Section 8.2 for details
- Procedures and sample collection (see Section 8.3 and Section 10.2)
    - Blood samples for:
        - Serology screening (HBV, HCV, HIV, and only if participant is HIV positive, CD4 count)
        - FVIII trough level (at least 72 hours after last pre-study FVIII infusion)
        - Factor VIII inhibitor (Section 8.10)
        - Laboratory evaluation (hematology and clinical chemistry)
- Training on and dispense of EPD device

Electronic patient diary (EPD) training and dispensing will also be done at the Screening visit after enrollment is completed and a study participant number is assigned. The EPD will be given to the participants or his caregivers to take home at any time between Screening and Baseline; however, participants/caregivers will be informed that no entries are to be made before the first infusion at Baseline.

In addition to the patient diary training at clinic visits, participants/caregivers will be told that study center staff will call each participant or parent/caregiver approximately every 2 weeks between Baseline and Visit 5 (Month 6) to verify proper completion of the participant diary and to review any new AEs and changes in concomitant medication since the last study visit and AEs.

7.1.2 Baseline/Visit 2 (No Later Than 6 Weeks From Visit 1)

The Baseline visit will include the following assessments and procedures:

- Inclusion/exclusion criteria verification, i.e., confirmation of eligibility including check of laboratory test results
  Note: Participants must have negative results from the central laboratory for

inhibitory antibodies against FVIII (<0.6 BU/mL determined with the Nijmegen-modified Bethesda assay)
- Height and weight for children/adolescents. Weight for adults.
- Physical examination
- Vital signs
- Concomitant medication review
- Blood sampling before administration of study drug intervention
  - FVIII inhibitor assessment (Section 8.10)
  - FVIII pre-infusion recovery (Section 7.3.2)
  - Laboratory evaluation (hematology, clinical chemistry)
- In-hospital administration of KOVALTRY
- Blood sampling after administration of study intervention (Section 7.3.2):
  - Incremental recovery (15 to 30 minutes post infusion)
- PK subset: Blood samples for PK assessments as outlined in Section 8.6
- Adverse events review
- Study drug dispensation for home infusions in accordance with IxRS drug dispensing schedule
- Diary training review. Participants or their caregivers will be instructed to complete the EPD as required (see Section 7.3.1) beginning at Baseline and through the end of the study (Visit 6).
- Begin regular bi-weekly contact between participant and the site to check EPD documentation and AE review until the End of Study/Early Termination

Although the first dose of study medication will be administered in the study center, additional study intervention supplies will be dispensed to participants or his caregivers for home infusions in accordance with IxRS drug dispensing schedule. Details of the study intervention provided are described in Section 6.

7.1.3 Visit 3/Month 1 (±7 Days)

At Visit 3, the following assessments and procedures will be performed as displayed in Section 1.3.1:

- Height and weight for children/adolescents
- Weight for adults
- Vital signs
- Concomitant medication review
- Review of EPD entries and bleeding history
- Blood sampling for Factor VIII inhibitor (Section 8.10)
- AE review
- Study drug dispensation for home infusions in accordance with IxRS drug dispensing schedule
- Return used and unused study intervention, drug accountability

- Continue regular bi-weekly contact between participant and the site to check EPD documentation and AE review until the End of Study/Early Termination

7.1.4 Visit 4/Month 2 (±7 Days)

At Visit 4 (Month 2), the following assessments and procedures will be performed as displayed in Section 1.3.1:

- Height and weight for children/adolescents
- Weight for adults
- Vital signs
- Concomitant medication review
- Review of EPD entries and bleeding history
- Blood sampling before administration of study drug intervention
    - FVIII inhibitor assessment (Section 8.10)
    - FVIII pre-infusion recovery (Section 7.3.2)
    - Laboratory evaluation (hematology, clinical chemistry)
- In-hospital administration of KOVALTRY
- Blood sampling after administration of study intervention (Section 7.3.2):
    - Incremental recovery (15 to 30 minutes post infusion)
- AE review
- Study drug dispensation for home infusions in accordance with IxRS drug dispensing schedule
- Return used and unused study intervention, drug accountability
- Continue regular bi-weekly contact between participant and the site to check EPD documentation and AE review until the End of Study/Early Termination

7.1.5 Visit 5/Month 6 (±7 Days)/Final Visit/Early Termination

At Visit 5 (Month 6 [±7 days]), the following assessments and procedures will be performed as described in Section 1.3.1:

- Height and weight (children and adolescents; weight only is obtained for adults)
- Physical examination
- Vital signs
- Concomitant medication review
- Blood sampling before administration of study drug intervention
    - FVIII inhibitor assessment (Section 8.10)
    - FVIII pre-infusion recovery (Section 7.3.2)
    - Laboratory evaluation (hematology, clinical chemistry)
- In-hospital administration of KOVALTRY
- Blood sampling after administration of study intervention (Section 7.3.2):
    - Incremental recovery (15 to 30 minutes post infusion)
- PK subset of adolescents/adults participants ≥12 years: Blood samples for PK assessments as outlined in Section 8.6

- Adverse events review
- Review of EPD entries and bleeding history (see Section 7.3.1) and return EPD
- Return used and unused study intervention, drug accountability

7.1.6 Follow-Up Call (+2 Weeks ±7 Days After the Final Visit)

For this telephone contact, each participant or caregiver will be asked about adverse events occurring since Visit 5 (6 months) and any concomitant medications including FVIII product used.

7.2 Study Visits - Part B (PUPs/MTPs)

Part B consists of a screening period followed by at least 50 ED per participant.

For MTPs, the Screening visit should only take place after a washout period of at least 72 hours following previous treatment with any FVIII replacement product.

The treatment period will last until 50 ED have been accumulated. The duration will vary and is dependent upon the frequency of prophylactic infusion and the number of bleeding events.

7.2.1 Visit 1/Screening

After obtaining signed Informed Consent from the prospective participant's parent or legal representative, as required, the following screening assessments will be performed:

- Inclusion/exclusion criteria verification
- Allocation of a unique participant number
- Review of eligibility requirements; no participant should receive study intervention unless all inclusion and exclusion criteria are met as listed in Section 5.1 and Section 5.2, respectively. Confirmation of selection criteria may be based on medical records for some conditions, but laboratory test results must be available for the listed items to confirm eligibility.
- Collect demographic data (e.g., age, sex [male only], race, etc.)
- Height/length and body weight (kg)
- Obtain a complete medical and surgical history (e.g., general, hemophilia, family history of hemophilia)
    - PUPs: Specific information on history of hemophilia (date of diagnosis, family history, FVIII level at diagnosis, treatment received for hemophilia, family history of past inhibitor formation, number and type of bleeding episodes in the last 12 months, and presence and location of target joints)
    - MTPs: Specific information on history of hemophilia (date of diagnosis, start of therapy, current FVIII product, number of ED, family history, FVIII level at diagnosis, history of inhibitor development, family history of past inhibitor formation, current treatment product and regimen, number and type of bleeding episodes in the last 12 months, and presence and location of target joints [defined as at least 3 spontaneous bleeding episodes into a single joint within a consecutive 6-month period])
- Prior medication (medication history), see Section 6.5
- Physical examination, see Section 8.1

- Vital signs (including systolic and diastolic blood pressure, heart rate, and body temperature); blood pressure may be deferred if the appropriate cuff size or equipment is not available (see Section 8.2 for details)
- Procedures and sample collection (see Section 8.3 and Section 10.2)
    - Blood samples for the following:
        - Baseline FVIII level (≥72 hours after the last pre-study FVIII infusion for MTPs)
        - FVIII inhibitor assessment (Section 8.10; not required for PUPs but required for MTPs)
        - Laboratory evaluation (hematology and clinical chemistry)
- Training on and dispensation of EPD device

EPD training and dispensation will also be done at the Screening visit after enrollment is completed and a study participant number is assigned. The EPD will be given to the parent/caregiver to take home at any time between Screening and Baseline; however, parents/caregivers will be informed that no entries are to be made before the first infusion at Baseline.

In addition to the EPD training at clinic visits, parents/caregivers will be told that study center staff will call each participant's parent/caregiver every 2 weeks between Baseline and the Final visit to verify proper completion of the participant diary and to review any new AEs and changes in concomitant medication since the last study visit.

7.2.2 Visit 2/Baseline (No Later Than 4 Weeks From Visit 1)

For MTPs, this visit will include the first administration of study drug.

For PUPs, the first dose of KOVALTRY may be for treatment of a bleed. First treatment should not occur during high risk situations, surgery, or bleeds requiring prolonged or intensive treatment (see Section 6.6.2).

The following activities will be performed:

- Inclusion/exclusion criteria verification, i.e., confirmation of eligibility including check of laboratory test results.
  Note: MTPs must be inhibitor negative as evaluated via local laboratory testing at the Screening visit. A confirmatory inhibitor test must be taken at least 1 week but not more than 2 weeks after the Screening visit. Results from local laboratory testing must be negative (<0.6 BU/mL) prior to administration of study intervention.
- Height/length and weight
- Vital signs (including systolic and diastolic blood pressure, heart rate, and body temperature); blood pressure may be deferred if the appropriate cuff size or equipment is not available (see Section 8.2 for details)
- Concomitant medication review
- Blood sampling before administration of study drug intervention
    - FVIII inhibitor assessment (Section 8.10; not required for PUPs but required for MTPs)

- In-hospital administration of the first dose of study drug (for MTPs and PUPs who are starting treatment at baseline).
  Note: First exposure to study drug may be either for treatment of an uncomplicated bleed or for start of prophylaxis. Inhibitor testing is mandatory every 3 to 5 ED until 20 ED are accumulated (see Section 6.6.2).
- Blood sampling after administration of study intervention (Section 7.3.2):
  - Incremental recovery (15 to 30 minutes post infusion) only for participants who start prophylaxis at Baseline; for PUPs who do not start prophylaxis at baseline, recovery should be done when prophylaxis is started
- AE review
- Study drug dispensation for home infusions in accordance with the IxRS drug dispensing schedule
- Diary training review; participants/caregivers will be instructed to complete the EPD as required (see Section 7.3.1) beginning at Baseline through the end of the study (see Section 4.4)
- Instruction on the prophylaxis regimen to be administered to the participant
- Begin regular biweekly contact between the participant's parent/caregiver and the site to check EPD documentation and AE review until the End of Study/Early Termination

It is recommended for PUPs to have the first dose of study intervention administered in the study center. Details of the study intervention provided are described in Section 6.

7.2.3 Visit 3/ED ~5 (4 ED ±1)

At Visit 3, the following assessments and procedures will be performed as displayed in Section 1.3.2.

- Height/length and weight
- Vital signs (see Section 8.2 for details)
- Concomitant medication review
- Review of EPD entries and bleeding history
- Blood sampling for laboratory tests
  - FVIII inhibitor assessment (Section 8.10)
  - FVIII:C trough level (≥48 hours after the last FVIII treatment)
- AE review
- Study drug dispensation for home infusions in accordance with the IxRS drug dispensing schedule
- Return used and unused study intervention (study drug accountability)
- Continue regular biweekly contact between the participant's parent/caregiver and the site to check EPD documentation and AE review until the End of Study/Early Termination

7.2.4 Visit 4/ED ~10 (9 ED ±1)

At Visit 4, the following assessments and procedures will be performed as displayed in Section 1.3.2.

- Height/length and weight
- Vital signs (see Section 8.2 for details)
- Concomitant medication review
- Review of EPD entries and bleeding history
- Blood sampling for laboratory tests
    - FVIII inhibitor assessment (Section 8.10)
    - FVIII:C trough level (≥48 hours after the last FVIII treatment)
- AE review
- Study drug dispensation for home infusions in accordance with the IxRS drug dispensing schedule
- Return used and unused study intervention (study drug accountability)
- Continue regular biweekly contact between the participant's parent/caregiver and the site to check EPD documentation and AE review until the End of Study/Early Termination

7.2.5 Visit 5/ED ~15 (14 ED ±1)

At Visit 5, the following assessments and procedures will be performed as displayed in Section 1.3.2.

- Height/length and weight
- Vital signs (see Section 8.2 for details)
- Concomitant medication review
- Review of EPD entries and bleeding history
- Blood sampling for laboratory tests
    - FVIII inhibitor assessment (Section 8.10)
    - FVIII:C trough level (≥48 hours after the last FVIII treatment)
- AE review
- Study drug dispensation for home infusions in accordance with the IxRS drug dispensing schedule
- Return used and unused study intervention (study drug accountability)
- Continue regular biweekly contact between the participant's parent/caregiver and the site to check EPD documentation and AE review until the End of Study/Early Termination

7.2.6 Visit 6/ED 20 (20 ED ±1)

At Visit 6, the following assessments and procedures will be performed as displayed in Section 1.3.2.

- Height/length and weight
- Vital signs (see Section 8.2 for details)

- Concomitant medication review
- Review of EPD entries and bleeding history
- Blood sampling for laboratory tests
    - FVIII inhibitor assessment (Section 8.10)
    - FVIII:C trough level (≥48 hours after the last FVIII treatment)
- In-hospital administration of study intervention
- Blood sampling after administration of study intervention (Section 7.3.2):
    - Incremental recovery (15 to 30 minutes post infusion)
- AE review
- Study drug dispensation for home infusions in accordance with the IxRS drug dispensing schedule
- Return used and unused study intervention (study drug accountability)
- Continue regular biweekly contact between the participant's parent/caregiver and the site to check EPD documentation and AE review until the End of Study/Early Termination

7.2.7 Visit 7/Interim Visit/30 to 40 ED

This visit is required only for PUPs and MTPs who have less than 40 ED 6 months after the Baseline visit. The intent is to have at least one scheduled visit between completion of 20 ED and the expected date of accumulating 50 ED. The primary purpose of the visit is to assess the well-being of the participant, ensure continued compliance with the treatment, and make any needed adjustments in dosage or infusion frequency based upon weight or bleeding events.

The following procedures and assessments will be performed:

- Height/length and weight
- Vital signs (see Section 8.2 for details)
- Concomitant medication review
- Review of EPD entries and bleeding history
- Blood sampling for laboratory tests
    - FVIII inhibitor assessment (Section 8.10)
    - FVIII:C trough level (≥48 hours after the last FVIII treatment)
- AE review
- Study drug dispensation for home infusions in accordance with the IxRS drug dispensing schedule
- Return used and unused study intervention (study drug accountability)
- Continue regular biweekly contact between the participant's parent/caregiver and the site to check EPD documentation and AE review until the End of Study/Early Termination

7.2.8 Final Visit/50 ED (+7 Days)/Early Termination

This visit will take place after 50 ED with study intervention are accumulated in participants who do not develop high titer FVIII inhibitor, or in the case of early termination. It is

expected that 50 ED will be achieved for most participants between 6 and 12 months after the start of prophylactic treatment.

The following procedures and assessments will be performed:

- Height/length and weight
- Physical examination
- Vital signs (see Section 8.2 for details)
- Concomitant medication review
- Review of EPD entries and bleeding history
- Blood sampling for laboratory tests
    - FVIII inhibitor assessment (Section 8.10)
    - FVIII:C trough level (≥48 hours after the last FVIII treatment)
- In-hospital administration of study intervention
- Blood sampling after administration of study intervention (Section 7.3.2):
    - Incremental recovery (15 to 30 minutes post infusion)
- AE review
- Return of EPD
- Return of used and unused study intervention for final study drug accountability

7.2.9 Follow-Up Call (2 Weeks ±7 Days After the Final Visit)

In this telephone contact, each participant's parent/caregiver will be asked about any new AEs and changes in concomitant medication, including FVIII products, since the last study visit.

7.3 Efficacy Assessments

The primary efficacy variable in Part A is the ABR of all bleeding episodes during prophylaxis. The ABR of all bleeding episodes within 48 hours of a previous prophylaxis infusion is the primary efficacy variable in Part B. The ABR of all bleeding episodes during prophylaxis in Part B and the ABR of all bleeding episodes within 48 hours of a previous prophylaxis infusion in Part A will be assessed as secondary efficacy parameters. Additionally, the ABR for the following efficacy variables will be summarized for both Part A and Part B:

- Treated bleeding episodes
- Joint bleeding episodes
- Joint bleeding episodes within 48h of previous prophylaxis infusion
- Target joint bleeding episodes
- Spontaneous bleeding episodes
- Spontaneous bleeding episodes within 48h of previous prophylaxis infusion
- Spontaneous joint bleeding episodes
- Trauma bleeding episodes
- Trauma bleeding episodes within 48h of previous prophylaxis infusion

Other efficacy variables include:

- Minor surgery bleeding control
- Participants'/parents'/physician's (in case of surgery) assessment of the response to treatment of bleeding episodes (excellent, good, moderate, or poor)
- The number of infusions required to treat a bleeding episode
- Factor VIII usage (expressed as number of infusions and IU/kg per year, as well as IU/kg per event)
- Extent of exposure in terms of exposure days (EDs)
- Type, location, and severity of bleeding episodes
- Reason for each infusion
- Incremental recovery

7.3.1 Treatment Logs/Bleeding Verification

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

Infusion of KOVALTRY

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

a. Date and time

b. Individual vial number (bar code scan from vial label or manual entry) and units administered

c. Reason for treatment:

- Prophylaxis
- Unscheduled prophylaxis (e.g., for physical activities, suspected or non-evident bleeding following identified trauma)
- Spontaneous bleeding first treatment
- Trauma bleeding first treatment
- Follow-up treatment
- Surgery
- ITI (only applicable to participants who develop high-titer inhibitor and received ITI)

Infusions of KOVALTRY as part of protocol mandated visits and procedures (e.g., for recovery and PK) will be recorded on the respective CRF pages.

Bleeding Episode

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

a. Date and time of onset

b. Type of bleeding (spontaneous, trauma, joint, muscle, skin/mucosal, internal, other)

c. Location

d. Intensity (mild, moderate, severe)

e. Treated [yes/no]:

If "yes": Date and time
Product used: KOVALTRY or other
Doses

If KOVALTRY is used for the treatment of a bleeding episode, the response to treatment (excellent, good, moderate, poor, too early to tell) must to be recorded. If "too early to tell" is entered, the participant will be queried for a response the next time the device is used.

For guidance to the participant or their caregiver, the following definitions for response to treatment are suggested. Individual participant 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, with at least one additional infusion for complete resolution
- **Poor (or None):** No improvement or condition worsens

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

- Information on study treatment administration must be captured in either the CRFs or in the EPDs, but not both. Information should not be duplicated.
- All use of study treatment outside the hospital/clinic should be recorded in the EPD.
- Use of study treatment in the hospital/clinic as defined in the protocol (e.g., at protocol-defined visits, for PK or recovery) should be recorded in the CRFs.
    - In the extremely unlikely event that an infusion at a protocol-defined visit is given for a bleeding, the information should be recorded in the EPD rather than the CRFs, since additional information needs to be collected for bleeding that is not collected in CRFs but only in the EPD.
    - 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).

7.3.2 Incremental Recovery of KOVALTRY

Incremental recovery will be determined by collecting a sample for KOVALTRY level before the scheduled infusion, and a second sample collected 15 to 30 min after end of the infusion.

Blood samples for KOVALTRY trough (predose) and recovery levels (15 to 30 min post infusion) will be collected in all participants at Visits 2, 4, and 5 in Part A; at Visits 2, 6, and 8 in Part B; and at additional time points based on the investigator's discretion. Infusions must be given in hospital and use the participants assigned treatment dose, rounded to full vial size.

The exact times for infusion and blood sampling before and after infusion and the dose administered will be documented in the CRF.

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

The samples will be collected as described in detail in the laboratory manual. All samples will be processed in the central laboratory (Part A) or local laboratory (Part B). Plasma concentrations of FVIII will be measured using a validated FVIII activity assay ("chromogenic assay" for Part A, "one-stage clotting assay" for Part B).

Samples for incremental recovery should be collected on days when the next prophylactic infusion is scheduled and at least 48 h after the last infusion prior to this. The measurements should only be performed when the participant is not actively bleeding and when FVIII:C levels are close to trough.

8. Safety Assessments

Planned time points for all safety assessments are provided in the SoAs (Section 1.3.1 for Part A and Section 1.3.2 for Part B).

The safety endpoints for the study include:

- 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 (Part A) or local laboratory (Part B).
- TEAEs
- Laboratory values and vital signs

The safety assessments for optional ITI treatment will be analyzed separately (see Section 9).

8.1 Physical Examination

- Physical examinations will be performed at Screening, Baseline, and at the Final visit/Early Termination visit.
    - A complete physical examination will include, at a minimum, assessments of the general appearance, dermatologic, head, eyes, ears, nose, mouth/throat/neck, thyroid, lymph nodes, cardiovascular, respiratory, gastrointestinal, extremities, neurological, and musculoskeletal, and review of systems.

- Investigators should pay special attention to clinical signs related to previous serious illnesses. Any abnormal finding should be documented.

- Height and weight will also be measured and recorded at the time points described in the SoAs (Section 1.3.1 for Part A and Section 1.3.2 for Part B). Body length will be measured instead of height, as age appropriate.

8.2 Vital Signs

- Vital signs will be measured at all visits. In case of any in-hospital infusion related AE, vital signs will be measured post-infusion for participants.
- Heart rate, body temperature, respiratory rate, and systolic and diastolic blood pressures will be assessed. Blood pressure may be deferred in infants if the appropriate size cuff or equipment is not available.
- Blood pressure and heart rate measurements should be preceded by at least 5 minutes of rest for the participant in a supine or seated position without distractions (e.g., television, cell phones).

8.3 Clinical Safety Laboratory Assessments

See Section 10.2 for the list of clinical laboratory tests to be performed and the SoAs (Section 1.3.1 for Part A and Section 1.3.2 for Part B) for the timing and frequency.

- The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the CRF. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings (based on the normal reference ranges supplied in investigator training) are those that are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.
- All laboratory tests with values considered clinically significantly abnormal during participation in the study should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the investigator.
    - If such values do not return to normal/baseline within a period of time judged reasonable by the investigator, the etiology should be identified and the Sponsor notified.
    - All protocol-required laboratory assessments, as defined in Section 1.3.1 and Section 1.3.2, must be conducted in accordance with the laboratory manual and the SoAs.
    - If laboratory values from non-protocol specified laboratory assessments performed at the institution's local laboratory require a change in participant management or are considered clinically significant by the investigator (e.g., SAE or AE or dose modification), then the results must be recorded in the CRF.

8.4 Adverse Events and Serious Adverse Events

As described in Section 10.3, an AE is any untoward medical occurrence in a patient or clinical study participant, associated with the use of study intervention, whether or not considered related to the study intervention. Detailed definitions and procedures for recording,

evaluating, follow-up, and reporting of all types of adverse events including SAEs can be found in Section 10.3. Events identified as adverse events of special interest (AESIs) for this study are specified in Section 8.4.7.

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

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE. They remain responsible for following up SAEs, AEs considered related to the study intervention or study procedures, or those that caused the participant to discontinue the study. Events of Special Interest have to be followed up regardless of causality or relationship to study intervention (see Section 8.4.7).

8.4.1 Time Period and Frequency for Collecting AE and SAE Information

All AEs and SAEs will be collected from the signing of the informed consent form (ICF) until the Follow-up call after the Final visit at the time points specified in the SoAs (Section 1.3.1 for Part A and Section 1.3.2 for Part B).

Medical occurrences that begin before the start of study intervention but after obtaining informed consent will be recorded on the AE Report Form of the case report form (CRF). Adverse events that in the opinion of the investigator occurred as a result of a study screening procedure will be considered non-treatment emergent adverse events and will be recorded as AEs in the eCRF.

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

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

8.4.2 Method of Detecting AEs and SAEs

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

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

8.4.3 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 AEs/SAEs/AESIs will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 6.9). Further information on follow-up procedures is provided in Section 10.3.

8.4.4 Regulatory Reporting Requirements for SAEs

- Prompt notification by the investigator to the Sponsor of an SAE within 24 hours is essential so that legal obligations and ethical responsibilities towards the safety

of participants and the safety of a study intervention under clinical investigation are met.

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

8.4.5 Pregnancy

Only male participants will be enrolled in this study ages <12 years and ≥12 to 65 years in Part A and <6 years in Part B. There is no target-related specific transport mechanism for KOVALTRY into semen or from semen into the conceptus. Following administration to a male participant, KOVALTRY would not be bioavailable via seminal delivery to the developing conceptus of an untreated partner. Therefore, no method of contraception is needed.

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

8.4.6 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 8.4.4).

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.*

8.4.7 Adverse Events of Special Interest (AESI)

The adverse events of special interest in this study are:

- Development of factor VIII inhibitors: It is mandatory that inhibitor development is assessed as "serious" and reported to the study Sponsor within 24 hours of awareness as a medical important event, following standards for SAE reporting.
- Hypersensitivity and allergic reactions including skin related and systemic reactions, such as anaphylactic reactions (seriousness should be a case by case decision).

8.5 Treatment of Overdose

Not applicable. No symptoms of overdose have been reported according to the Prescribing Information (see Section 12).

8.6 Pharmacokinetics

PK assessments will be performed in Part A only.

The PK assessments are planned in a subset of 12 children <12 years and in 12 adolescents/adults ≥12 years. For participants <12 years old, the study would strive for balance between the two subgroups (<6y and 6 to <12y).

Based on the observed PK of KOVALTRY in prior studies, it is expected that a reduced sampling strategy will be sufficient to calculate relevant PK parameters in children below 12 years reliably.

For the PK of KOVALTRY assessment, participants will be administered a dose of 50 IU/kg. The participant must have no signs or symptoms of an acute bleeding episode. Measurement of FVIII activity of KOVALTRY will be done pre-infusion, 15 to 30 min, 4h, and 24 h post-infusion in children below 12 years and pre-infusion, 10 to 15min, 30min, 1h, 4h, 6 to 8h, 24h, and 30 to 48h in adolescent/adult participants. Samples should be collected as close as possible to the designated sampling times and at least 48 hours after previous treatment to ensure that pre-infusion KOVALTRY levels are measured at trough. If there is a delay in collecting a sample, it should still be collected. In all cases, the exact time of start and end of infusion and the time of actual sample collection should be noted in the CRF. Infusion doses for PK measurements and recovery should be given at the study center and directly reported in CRF.

The actual sampling times will be used for PK evaluation. Deviations from planned PK blood sampling times are not considered protocol deviations.

All samples will be processed in the central laboratory.

For children below 12 years, the evaluation of PK of KOVALTRY is only required once and should be performed at Visit 2.

For adolescents/adult participants 12 years or older, two PK profiles for the evaluation of PK of KOVALTRY are required. The first PK profile should be performed with start of treatment

with KOVALTRY at Visit 2. The second PK profile should be performed after approximately 6 months of treatment at Visit 5.

Based on the plasma concentration time data, the following PK parameters will be derived: C_{max}, AUC, AUC_{norm}, $AUC_{(0\text{-t last})}$, $AUC_{(0\text{-t last}) norm}$, $C_{max\ norm}$, clearance, MRT, V_{ss}, and $t_{½}$.

Details about the collection, processing, storage, and shipment of samples will be provided separately (e.g., sample handling sheets or laboratory manual).

8.7 Pharmacodynamics

Pharmacodynamic parameters are not evaluated in this study.

8.8 Genetics

Genetics are not evaluated in this study.

8.9 Biomarkers

Biomarkers are not evaluated in this study.

8.10 Immunogenicity Assessments

8.10.1 Part A (PTPs) Immunogenicity Assessments

All participants in Part A will be tested for Factor VIII inhibitor development at Screening, Baseline (Day 1), Visit 3, Visit 4, and Visit 5 (Month 6, End of Study/Early Termination), or in case of suspicion of Loss of Efficacy (LoE).

FVIII inhibitor testing will be done according to the Nijmegen-modified Bethesda assay. A positive inhibitor test is defined with a threshold of ≥0.6 BU at the central laboratory. If an inhibitor to the study drug (KOVALTRY) is detected after the participant has started treatment with study drug, 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.

8.10.2 Part B (PUPs/MTPs) Immunogenicity Assessments

In Part B, the requirement for FVIII inhibitor testing before start of study treatment at Screening and Baseline will only be done in MTPs; this assessment is not applicable for PUPs. The absence of inhibitors will be assessed by local laboratory testing at Screening (<0.6 BU/mL) of 2 consecutive samples at least 1 week but not more than 2 weeks apart.

After study treatment is started, PUPs/MTPs must be tested for development of inhibitor to study drug (KOVALTRY) at Visit 3 [approximately 5 ED], Visit 4 [approximately 10 ED], Visit 5 [approximately 15 ED], Visit 6 [approximately 20 ED], Visit 7/Interim visit [approximately 30 to 40 ED], and Visit 8/Final visit [50 ED]/Early Termination). The first positive inhibitor test must be confirmed by analysis of a second sample and by analysis of FVIII level recovery within 2 weeks of notification. After confirmation of the positive result, the inhibitor development will be reported as SAE.

8.11 Health Economics

Health Economics parameters are not evaluated in this study.

9. Statistical Considerations

In order to reduce the risk generally associated with open-label trials, the final SAP will be available before the first participant first visit.

9.1 Statistical Hypotheses

The study is not designed to test any predefined hypothesis. The statistical analysis planned for the study is aimed to follow the analyses of the completed LEOPOLD studies and will be descriptive. The Statistical Analysis Plan (SAP) will provide the details of all planned analyses.

9.2 Sample Size Determination

9.2.1 Sample Size Determination in Part A (PTPs)

The primary variable "annualized bleeding rate (ABR)" is used for the evaluation of the efficacy. The mean ABR for total bleeding episodes for previously treated severe hemophilia A study participants <12 years of age receiving prophylaxis with KOVALTRY in completed LEOPOLD Kids Part A study was 3.75 ± 4.98 (median (Q1; Q3): 1.90 (0.00; 6.02)).[11] Assuming that the average ABR for this patient population is 4 bleeding episodes and the standard deviation is 5 bleeding episodes per year, a sample size of 30 participants will allow estimating ABR by means of a 95% confidence interval with a half-width of 1.8 (the confidence interval is 2.2-5.8) which will consider to provide reasonable precision on the estimations.

For the previously treated adult/adolescent treatment arm, the proposed sample size of 12 participants is adequate for collection of PK data and will also allow for collection of supplemental efficacy and safety data in this population.

The sample size (30 children + 12 adolescents and adults) has been confirmed in consultation with China CDE as adequate to provide additional clinical data for comprehensive evaluation of efficacy, safety, and PK of KOVALTRY in Chinese hemophilia A patients.

9.2.2 Sample Size Determination in Part B (PUPs/MTPs)

To fulfill the post-approval commitment enforced for KOVALTRY, the Sponsor is committed to collecting additional efficacy and safety data in previously untreated Chinese severe hemophilia A patients, in line with the CDE Technical Guideline on the Clinical Investigation of Recombinant Human Coagulation Factor VIII.

It is considered feasible to enroll approximately 6 PUPs/MTPs in Part B of this study.

Part B of this study is designed in accordance with the multinational clinical trial of KOVALTRY in previously untreated/minimally treated patients, LEOPOLD Kids Part B, where the annualized number of bleeds that occur within 48 hours after a prophylaxis infusion was the primary efficacy endpoint.

A mean of 1.9 (standard deviation 3.3) was observed for this ABR in LEOPOLD Kids Part B. Assuming the same distribution, the point estimate for the ABR within 48 hours after a prophylaxis infusion of 6 patients will be smaller than 2.9 with a probability of more than 80% (based on simulations of data for 6 patients from a negative binomial distribution).

In addition, in the SIPPET study[14] (a multinational, prospective, randomized trial that assessed the incidence of FVIII inhibitors among PUPs treated with plasma-derived FVIII

containing von Willebrand factor or rFVIII products), the incidence of inhibitor development for the class of rFVIII products was 44.5% (95% CI: 34.7% to 54.3%).

Therefore, the true inhibitor rate for PUPs/MTPs is assumed to be within the range of 35% to 54%. With a sample size of 6 PUPs/MTPs, there is at least 92% power to observe at least 1 participant developing an inhibitor if the rate is between 35% and 54%. In case an event of inhibitor development is not observed, this sample size would provide more than 90% reassurance that the inhibitor rate should be no more than 35%.

9.3 Populations for Analyses

For purposes of analysis, the following populations are defined in Table 9–1.

Table 9–1: Analysis Populations

Population	Description
Enrolled	All participants who signed the ICF or had an ICF signed on their behalf by a parent or legal representative.
Safety	Participants enrolled into the study and received at least 1 dose of study drug. The safety population will be used for the safety analysis.
Modified Intent-to-Treat (mITT)*	All study participants who have infusion/bleeding data from the EPD and/or CRF. The mITT population will be used for the efficacy analysis.
Per Protocol (PP)**	All mITT participants who completed study treatment and have at least 50 exposure days on study, without major protocol deviations.
PK analysis population	All participants with evaluable PK data will be included in the analysis of pharmacokinetic data.
ITI treatment analysis population	All participants who enter ITI treatment with study intervention will be included in the analysis for ITI treatment.

* The ITT is inclusive of all enrolled and eligible patients. Modified ITT was introduced for this study as there is an additional condition that is to be met for participants included in ITT. This condition is that study participants need to have infusion/bleeding data from the EPD and /or CRF. Therefore, ITT analysis population is renamed “modified ITT” for this study.

** Only to be used if at least 5% of mITT participants (<12 or ≥12 years of age) are excluded from the PP population. The PP population is only in Part A; Part B will not have a PP population.

9.4 Statistical Analyses

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

9.4.1 General Considerations

There is no confirmatory comparison planned for this study; study results will be numerically evaluated and compared with the data in the completed LEOPOLD Clinical Trials.

Efficacy analyses outlined in this section only include the data from Part A or Part B (i.e., data from the Optional ITI Treatment are excluded).

For the efficacy endpoints, bleeding events will be presented as summary statistics by age groups.

The annualized bleeding rates for each participant are estimated via

Annualized bleeding rate [per year] =
365.25 [days per year] x (# of bleeding episodes in treatment period) / duration of treatment period [in days]

The treatment period is defined as from the date and time of first study treatment until the date and time of last infusion of study medication, or last visit, whichever is later (not including the Optional ITI Treatment). Before this period is the screening period, after this period is the follow-up period.

Further, for the derivation of analysis variables for bleeding episodes, the following rules will apply:

- "24-hour rule":
  No more than 1 bleeding episode in a calendar day is counted. If there is more than 1 bleeding episode in a calendar day, to determine which bleeding episodes are counted, priority is given to treated bleeding episodes, spontaneous or trauma bleeding episodes, then joint bleeding episodes. Otherwise, the first bleeding episode in the day is counted. Severity and treatment response will be the worst value of the bleeding episodes of the day. The bleeding site will be aggregated over all bleeding events from that day.
- "72-hour rule":
  A spontaneous joint or spontaneous muscle bleeding episode will not be counted if it occurs within 72 hours of a prior bleeding episode (or infusion for that bleeding episode) at the same site. For a bleeding episode to be affected by this rule, all sites listed for the bleeding episode must be the same sites specified in the previous bleeding episode. If the current and previous bleeds are both skin/mucosa bleeds, this rule does not apply. Infusions for such bleeding episodes will be considered to be follow-up infusions.

Missing information on date and time of bleeding episodes will be substituted by the date and time of first treatment, if available.

Further handling of missing data will be described in the SAP.

9.4.2 Primary Endpoint(s)

All efficacy analyses will be performed on the mITT population. In case of PP population (Part A only), more than 5% of participants in one arm (children or adolescents/adults) are excluded from the mITT population, and analyses for primary and secondary endpoints will be repeated in the PP population. As the non-adherence to the EPD documentation is considered independent from the treatment efficacy, the exclusion of participants without bleeding/infusion data from the EPD does not interfere with the intention-to-treat principle. These participants are excluded in order not to dilute the treatment effect.

The primary endpoint in Part A is the ABR of all bleeding episodes during prophylaxis treatment, and it will be summarized by age group (<12 y, ≥12 y) separately.

The primary endpoint in Part B is the ABR of all bleeding episodes within 48 hours of a previous prophylaxis infusion.

9.4.3 Secondary Endpoint(s)

Spontaneous bleeding episodes, trauma bleeding episodes, joint bleeding episodes, and other bleeding episodes types will be summarized separately.

Other efficacy variables are:

- ABR of treated bleeding episodes
- ABR of target joint bleeding episodes
- ABR of bleeding episodes within 48h of previous prophylaxis infusion (total, joint, spontaneous, trauma) [for Part A]
- ABR of all bleeding episodes during prophylaxis treatment [for Part B]
- Study participant's/caregiver's assessment of response to treatment of bleeding episodes (excellent, moderate, good, or poor)
- Physician's assessment of the response to treatment of bleeding episodes in minor surgery (excellent, moderate, good, or poor)
- Evaluate proportion of patients without bleeding episodes
- The number of infusions per bleeding episode
- Factor VIII usage (expressed as number of infusions and IU/kg per year, as well as IU/kg per event)
- Incremental recovery

All details of the analysis will be provided in the SAP.

9.4.4 Safety Analyse(s)

Safety analysis will be performed separately for Part A, Part B, and Optional ITI Treatment.

Safety data will be summarized for all participants in the safety population for overall and by age groups respectively for Part A and summarized for Part B. Laboratory findings, AEs, concomitant medications, vital signs, and medical history data will be provided in participant listings. Laboratory values and vital signs will be summarized.

Individual listings of AEs (including age, AEs as reported, start, duration, severity, relation to study drug) will be provided. An AE is defined as treatment-emergent if it started or deteriorated after the first infusion and not later than three days after the last infusion in Part A or Part B. The incidence of treatment-emergent AEs will be summarized using the Medical Dictionary for Regulatory Affairs (MedDRA).

Inhibitor development as measured by Nijmegen-modified Bethesda assay will be summarized by time point and presented in participant listings. The purpose of the listing is to delineate the clinical factors that may be positively associated with development of the inhibitor. Confirmation of the first positive inhibitor titer (Bethesda ≥0.6 BU/mL) will require repeat measurement of a second different sample.

If the repeated inhibitor result is <0.6 BU/mL without intervention, the inhibitor is not confirmed and should not be reported as an SAE. Inhibitors will be classified as being either low titer (≥0.6 BU/mL and ≤5 BU/mL) or high titer based upon persistence of an inhibitor >5 BU/mL. Proportions of participants with inhibitor will be presented in an overview table. Exact Clopper Pearson CI for the proportion will be given if any inhibitor exists.

The rate of inhibitor development will be summarized and described for both the pediatric and the adolescent/adult populations, and for the overall study population combined.

Safety analysis for optional ITI treatment is based on the ITI treatment set. Laboratory findings (inhibitor titer and recovery), AEs, concomitant medications, and EDs will be provided in participant listings. More details will be provided in the SAP.

9.4.5 Pharmacokinetic Analyses

Pharmacokinetic analyses will be described in the statistical analysis plan finalized before FPFV.

In addition, the pharmacokinetic data collected during this study might be analyzed by means of a population PK approach. The results of this evaluation may be reported in a separate Modeling and Simulation report. The actual sampling times will be used for PK evaluation.

9.5 Interim Analyses

In case the study will not be completed at the time of next KOVALTRY license renewal application in China, the most current results will be delivered for license renewal, and an interim analysis will be performed with all available data. This approach has been agreed with CDE.

9.6 Data Monitoring Committee (DMC)

Not applicable to this study.

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.
- Regulations on Management of Human Genetic Resources of the People's Republic of China.
- The protocol, protocol amendments, ICF, Prescribing Information, Investigator Brochure, and other relevant documents (e.g., advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.

The investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
- Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
- Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations

10.1.2 Informed Consent Process

- The investigator or his/her representative will explain the nature of the study to the participant or his parent, guardian, or legally authorized representative and answer all questions regarding the study.
- For minors, consent shall be given by the parents/legal representative. The assent of a minor shall also be requested where such a person is able to express his own will. His refusal or the withdrawal of his consent may not be disregarded.
- The informed consent form and any other written information provided to participants/legal representatives will be revised whenever important new information becomes available that may be relevant to the participants'/parents' consent, or there is an amendment to the protocol that necessitates a change to the content of the participant information and/or the written informed consent form. The investigator will inform the participant/legal representative of changes in a timely manner and will ask the participant to confirm his participation in the study by signing the revised informed consent form. Any revised written informed

consent form and written information must receive the IEC/IRB's approval / favorable opinion in advance of use.

- Participants must be informed that their participation is voluntary. Participants or their legally authorized representative will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study center.
- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Participants must be re-consented to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the participant or the participant's legally authorized representative.

10.1.3 Data Protection

- Participants will be assigned a unique identifier by the Sponsor. Any participant records or datasets that are transferred to the Sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.
- The participant must be informed that his personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant 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 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.

10.1.4 Committees Structure

Not applicable to this study.

10.1.5 Dissemination of Clinical Study Data

The Clinical Study Report (CSR) will be written within 1 year of the end of study and sent to the involved ECs and Regulatory Authorities. It will be reviewed and approved by the Coordinating Investigator as required by local authorities.

The Sponsor will ensure required disclosure of CSRs, periodic safety reports, and clinical study summary reports after review by regulatory authorities, including CSRs from studies with negative outcomes and from terminated development programs and posting of company-sponsored study information and tabular study results on the US National Institutes of Health's website www.ClinicalTrials.gov and other publicly-accessible sites.

Publication planning and other activities related to non-promotional, peer-reviewed publications to ensure the scientific integrity and credibility of publication activities may be performed by the Sponsor.

The Sponsor may also grant access to analyzable datasets from clinical studies through a secure system, following an independent assessment of the scientific merit of a rigorously defined research question from a third party.

10.1.6 Data Quality Assurance

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

10.1.7 Source Documents

Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator’s site.

Data reported in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available. Definition of what constitutes source data can be found in the Study/Site source data identification checklist.

10.1.8 Study and Site Start and Closure

The study start date is the date on which the clinical study will be open for recruitment of participants.

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

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

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

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

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 participant therapy and/or follow-up.

10.1.9 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 or within 1 year post clinical study close/end of study participation.

10.1.10 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

Table 10–1 shows the estimated total blood volume for children 1-10 kg and the recommended amount of blood for study purposes. These volumes should be considered a guideline, and may be exceeded if determined to be safe by the investigator.

Table 10–1: Recommended Blood Draw Volume

Body Wt. (kg)	Body Wt. (lbs)	Total blood volume (mL)	Allowable volume (mL) in one blood draw (1% of total blood volume)	Total volume (mL) drawn in a 30-day period (3% of total blood volume)
1	2.2	100	1	3
2	4.4	200	2	6
3	6.3	240	2.4	7.2
4	8.8	320	3.2	9.6
5	11	400	4	12
6	13.2	480	4.8	14.4
7	15.4	560	5	16.8
8	17.6	640	6.4	19.2
9	19.8	720	7.2	21.6
10	22	800	8	24

Abbreviations: Wt.: Body weight
Source: (15)

For infants of at least 7 kg at study enrollment, the volumes listed for each individual visit should be well tolerated.

The tests described in Section 8.3 and listed in Table 10–2 will be performed by the central laboratory (Part A, investigators will be provided with a laboratory manual for instructions on how to collect and process samples) or local laboratory (Part B). For part A if a local sample analysis is required, it is important that the sample for central analysis is obtained at the same time. Additionally, if the local laboratory results are used to make either a study intervention decision or response evaluation, the results must be entered into the CRF. For part B, a separated page for local laboratory results will be available in eCRF.

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 10–2: Protocol-Required Safety Laboratory Assessments

Laboratory Assessments	Parameters			
Hematology	Platelet count	White blood cell (WBC) count with differential (neutrophils, lymphocytes, monocytes, eosinophils, basophils)		
	Erythrocyte count			
	Hemoglobin			
	Hematocrit			
Clinical chemistry	Blood urea nitrogen (BUN)	Potassium	Aspartate aminotransferase (AST)	Total bilirubin
	Creatinine	Sodium	Alanine aminotransferase (ALT)	Total protein
	Albumin	Chloride (Cl)	Bicarbonate (CO_3)	Lactate dehydrogenase (LDH)
Other tests	• HCV, HBV, and HIV antibody (for screening only); CD4 count for patients who are HIV positive • Factor VIII inhibitor • Factor VIII level			
Notes:	• All routine study-required laboratory assessments will be performed by a central lab for Part A, the exception of some samples sent by central lab to an independent specialty lab for required tests of FVIII level and FVIII inhibitors. All routine study-required laboratory assessments will be performed by local lab for Part B. • The results of each test will be transferred into the clinical database.			

Investigators must document their review of each laboratory safety report.

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

10.3.1 Definition of AE

AE Definition

- An AE is any untoward medical occurrence in a patient or 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 drug-drug interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.
- “Lack of efficacy” or “failure of expected pharmacological action” per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfills the definition of an AE or SAE.

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

- Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant’s condition.
- The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant’s condition.
- Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the procedure is the AE. If a procedure is performed prior to study

start, then associated AEs are not reported as AEs, unless the associated condition has deteriorated since study initiation.

- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.
- Any bleeding event occurring during the study will not be documented as an AE, because this is captured in the assessment of efficacy. However, if the bleeding fulfills the criterion for an SAE (e.g. results in hospitalization), then the event should be recorded and reported as an SAE.

10.3.2 Definition of SAE

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (e.g., hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

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

a. Results in death

b. Is life-threatening

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

c. Requires inpatient hospitalization or prolongation of existing hospitalization

- In general, hospitalization signifies that the participant has been detained (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 disability/incapacity

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

e. Is a congenital anomaly/birth defect

f. Other situations/medical important event:

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

Action taken with study treatment:

- Action taken with study treatment
- Any action on study treatment to resolve the AE is to be documented using the categories listed below.
    - Drug withdrawn
    - Drug interrupted
    - Dose reduced
    - Dose not changed
    - Dose increased
    - Not applicable
    - Unknown

The outcome of the AE is to be documented as follows:

- Recovered/resolved
- Recovering/resolving
- Recovered/resolved with sequelae
- Not recovered/not resolved
- Fatal
- Unknown

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

AE and SAE Recording

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (e.g., hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The investigator will then record all relevant AE/SAE information in the CRF.
- It is not acceptable for the investigator to send photocopies of the participant's medical records to Sponsor in lieu of completion of the AE/SAE CRF page.

- There may be instances when copies of medical records for certain cases are requested by 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 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.
- Each event should be described in detail along with start and stop dates, severity, relationship to investigational product, action taken, and outcome

Assessment of Intensity

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

Assessment of Causality

An Adverse Reaction (AR) is defined as a response to a medicinal product which is noxious and unintended. An AR is any AE judged as having a reasonable suspected causal relationship to the medicinal product

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

- The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE.
- A “reasonable possibility” of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated.
- The investigator will also consult the Investigator’s Brochure (IB) and/or Product Information, for marketed products, in his/her assessment.

- For each AE/SAE, the investigator **must** document in the medical notes that he/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.
- If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide to the Sponsor with a copy of any post-mortem findings including histopathology.
- New or updated information will be recorded in the originally completed CRF.
- The investigator will submit any updated SAE data to the Sponsor within 24 hours of receipt of the information.

10.3.4 Reporting of SAEs

Starting with the signature of the informed consent, all non-serious adverse events (AE) must be documented on the AE Report Form or in the CRF / electronic data capture (EDC) system and forwarded to the MAH within 7 calendar days (for EU countries or if required by local regulations of participating country) / 60 days (for countries outside the EU) of awareness. All serious AEs (SAE) must be documented and forwarded immediately (within 24 hours of awareness). For each AE, the physician must assess and document the seriousness, duration, relationship to product, action taken and outcome of the event.

SAE Reporting to Sponsor via an Electronic Data Collection Tool

- The primary mechanism for reporting an SAE to Sponsor will be the electronic data collection tool.
- If the electronic system is unavailable, then the site will use the paper SAE data collection tool (see next section) in order to report the event within 24 hours.
- The site will enter the SAE data into the electronic system as soon as it becomes available.

- After the study is completed at a given site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information on a paper SAE form (see next section) or to the Sponsor´s Medical Expert by telephone.
- Contacts for SAE reporting can be found in Investigators' Site File.

SAE Reporting to the Sponsor via Paper CRF

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

10.4 Appendix 4: A Guide for Dosing for Bleeding and Surgery

Table 10–3: Dosing for Control of Bleeding Episodes

Degree of Bleeding	Factor VIII Level Required (IU/dL or % of Normal)	Frequency of Doses (hours)	Duration of Therapy (days)
Minor (early hemarthrosis, minor muscle, oral bleeding)	20–40	Repeat every 12–24 hours	At least 1 day, until bleeding episode as indicated by pain is resolved or healing is achieved
Moderate (more extensive hemarthrosis, muscle bleeding, or hematoma)	30–60	Repeat every 12–24 hours	3 to 4 days or more until pain and acute disability are resolved
Major (intracranial, intra-abdominal or intrathoracic hemorrhages, gastrointestinal bleeding, central nervous system bleeding, bleeding in the retropharyngeal or retroperitoneal spaces, or iliopsoas sheath, life or limb threatening hemorrhage)	60–100	Repeat every 8–24 hours	Until bleeding is resolved

Table 10–4: Dosing for Perioperative Management

Type of Surgery	Factor VIII Level Required (IU/dL or % of Normal)	Frequency of Doses (hours)	Duration of Therapy (days)
Minor (such as tooth extraction)	30–60 (pre- and post-operative)	Repeat every 24 hours	At least 1 day until healing is achieved
Major (such as intracranial, intra-abdominal, intrathoracic, or joint replacement surgery)	80–100 (pre- and post-operative)	Repeat every 8–24 hours	Until adequate wound healing is complete, then continue therapy for at least another 7 days to maintain Factor VIII activity of 30%–60% (IU/dL)

Table 10–5: Definition of Adequacy of Hemostasis for Surgical Procedures

Excellent	Intraoperative and postoperative blood loss similar (within 10%) to that in the non-hemophilic patient. • No extra (unplanned) doses of FVIII/bypassing agent needed **and** • Blood component transfusions required are similar to those in a non-hemophilic patient
Good	Intraoperative and/or postoperative blood loss slightly increased over expectation for the non-hemophilic patient (between 10% and 25% of expected), but the difference is judged by the involved surgeon/anesthetist to be clinically insignificant. • No extra (unplanned) doses of FVIII /bypassing agents needed **and** • Blood component transfusions required are similar to those in the non-hemophilic patient
Moderate (Fair)	Intraoperative and/or postoperative blood loss increased over expectation (25% to 50%) for the non-hemophilic patient, and additional treatment is needed. • Extra (unplanned) dose of FVIII /bypassing agents needed **or** • Increased blood component (within 2-fold) of the anticipated transfusion requirement
Poor	Significant intraoperative and/or postoperative blood loss that is substantially increased over expectation (>50%) for the non-hemophilic patient, requires intervention, and is not explained by a surgical/medical issue other than hemophilia. • Unexpected hypotension or unexpected transfer to intensive care unit (ICU) due to bleeding **or** • Substantially increased blood component (>2-fold) of the anticipated transfusion requirement

Abbreviation: FVIII = factor VIII
Source: (16)
Notes:

1. If required for minor surgery or emergency major surgery, Kovaltry infusions will be recorded in the case report form (CRF). The doses infused and the frequency of repeat treatment will be collected. The surgeon or interventionalist will be asked to compare estimated blood loss from experience with non-hemophilic patients undergoing comparable procedures, and assess intraoperative efficacy at the end of the procedure. Post-surgical efficacy will be assessed at least 24 h after the first dose of Kovaltry has been given by surgical staff at drain removal, if required, and by the hematologist at discharge.
2. Data on blood loss will be collected, as estimated at the time of surgery, change or drop in hemoglobin/hematocrit, the need for additional or other hemostatic medications, and the type and number of blood products transfused. Hemostatic-related surgical complications will also be obtained including data on specific diagnostic evaluations needed (e.g., imaging to follow the size of a hematoma).

10.5 Appendix 5: Optional Immune Tolerance Induction Treatment

10.5.1 Optional ITI Treatment for Participants who Develop High-Titer Inhibitors During the Study

If the option to receive ITI with the study intervention is made, the participant will discontinue participation in either Part A or Part B and continue in the Optional ITI Treatment, during which ITI will be provided at a dose of up to 200 IU/kg daily for up to a maximum of 18 months or until failure. A separate signed informed consent is required.

Initiation of ITI therapy (ITI Visit 1) should occur no later than 4 weeks from the date of notification by the investigator of the high-titer inhibitor development. In patients with a peak inhibitor titer >10 BU/mL, it is recommended to postpone initiation of ITI until the inhibitor titer drops to ≤10 BU/mL. It is recommended to monitor the inhibitor titer monthly. In patients with a peak inhibitor titer >10 BU/mL who experience serious or life-threatening bleeding or have frequent mild to moderate bleeding and are being considered for bypassing agent prophylaxis, an earlier start to ITI may be considered to avoid the morbidity associated with ongoing bleeding.

Response to ITI therapy may be observed earlier than 18 months and is defined as having no detectable inhibitor based on Nijmegen assay (<0.6 BU/mL) and FVIII recovery of >66% of predicted value. Failure is defined as no response (<20% decrease in the inhibitor level) within a 6-month period after the initial 3 months of ITI and in the absence of any infection. In case of failure, ITI should be discontinued, and the Early ITI Termination visit will occur.

During the Optional ITI Treatment, failure to adhere to follow-up visits as per protocol (see Section 10.5.2) will lead to discontinuation of ITI support.

At the investigator's discretion, the participant may stop ITI with study drug. The Early ITI Termination visit should be done if the decision is made by the investigator/participant to stop ITI prior to documented negative inhibitor titer.

For analysis of Optional ITI Treatment data, see Section 9.3, Section 9.4.1, and Section 9.4.4. Efficacy (ABR) will not be analyzed for ITI patients. Safety will be analyzed separately for the ITI treatment set.

10.5.2 Optional ITI Treatment - Schedule of Activities

Assessments	ITI Visit 1[a]	ITI Visit 2[a] Month 2	ITI Visit 3[a] Month 4	ITI Visit 4[a] Month 6	ITI Visit X[a] Month X	Confirmatory Visit[b]	Final ITI Visit[c]/ Early ITI Termination Visit[d]
Informed consent	X						
Study drug dispensation[e]	X	X	X	X	X	X	
ITI treatment accountability		X	X	X	X	X	X
EPD documentation and review (continuously)[f]	X	X	X	X	X	X	X
FVIII inhibitor testing[d]	X	X	X	X	X	X[c]	
Recovery (FVIII level)[d, g]						X[c]	
Adverse events	X	X	X	X	X	X	X
Concomitant medications (continuously)[h]	X	X	X	X	X	X	X
Phone calls[i]		X	X	X	X	X	

Abbreviations: CRF = case report form; EPD = electronic patient diary; FVIII = factor VIII; ITI = immune tolerance induction; RAVE = data base for electronic case report

a ITI visits should be performed every 2 months until the first negative inhibitor titer of <0.6 BU/mL.
b A confirmatory inhibitor testing and recovery evaluation should be performed within 1 month after the first negative testing. After the first negative testing, ITI treatment will continue until result of the second (confirmatory) inhibitor testing is obtained. At the discretion of the investigator, participants may stop ITI treatment without a second (confirmatory) inhibitory testing.
c The Final ITI visit will occur 2 weeks (±7 days) after the notification of the second (confirmatory) negative inhibitor testing and recovery.
d Participants who undergo the Early ITI Termination visit are recommended to have FVIII inhibitor testing and recovery evaluation.
e Drug dispensing will be done in accordance with the individual drug dispensing schedule every 28 days (±7 days).
f ITI treatment and bleeding episodes will be entered into the EPD.
g Blood samples for FVIII level will be taken pre-infusion and at 15 to 30 minutes after end of infusion to calculate recovery. Infusion doses for recovery measurements must be given in hospital and directly reported in RAVE. The bioanalysis will be done at a central laboratory (Part A) or local laboratory (Part B).
h Bypassing agents will be entered into the concomitant medications page of the CRF.
i Study center staff will call the participant or parent/caregiver approximately every 4 weeks between ITI visits to review any new adverse events and changes in concomitant medication since the last ITI visit.

10.5.3 Chinese Hemophilia Society Guideline for ITI

Please refer to (17).

10.6 Appendix 6: Abbreviations

ABR	Annualized bleeding rate
ALT	Alanine Aminotransferase
AE	adverse event
AESI	adverse event of special interest
AST	Aspartate Aminotransferase
AUC	area under the plasma concentration vs time curve from zero to infinity after single (first) dose
AUC_{norm}	area under the plasma concentration by the standard normative distribution
$AUC_{(0\text{-t last})}$	AUC from time 0 to the last data point
$AUC_{(0\text{-t last}) norm}$	Up to the last measurable concentration (otherwise called AUC_{last} by the standard normative distribution)
BU	Bethesda Unit
BHK	Baby Hamster Kidney
CD4	cluster of differentiation 4
CDE	Center for Drug Evaluation
CFR	Code of Federal Regulations Title 21
C_{max}	maximum concentration of FVIII in plasma
CRF	case report form (either paper or electronic)
CSR	Clinical study report
CVAD	central venous access devices
ECG	electrocardiography
eCRF	electronic case report form
ED	exposure days
e.g.	*exempli gratia*, for example
EPD	Electronic patient diary
EU	European Union
FPFV	First Patient First Visit
FVIII	human coagulation factor VIII
FVIII:C	factor VIII concentration
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
HBV	hepatitis B virus
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HSP	human heat shock protein
ICF	informed consent form
ICH	International Conference on Harmonization
ICU	intensive care unit
i.e.	*id est,* that is
IEC	Independent Ethics Committee
IRB	Institutional Review Board
ITI	immune tolerance induction
ITT	intent to treat
IU	international units
IV	Intravenous
IxRS	Interactive voice/web Response System
kg	kilogram
LD	Lactate Dehydrogenase
MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified Intent-to-Treat
MRT	mean resistance time
MTPs	minimally treated patients
NMPA	National Medical Products Administration
PI	Principle Investigator or Package Insert

PK	pharmacokinetics
PTPs	previously treated patients
PUPs	previously untreated patients
RAVE	data base for electronic case report
rFVIII	recombinant coagulation factor VIII
SAE	serious adverse event
SAP	statistical analysis plan
SUSAR	suspected unexpected serious adverse reactions
TMF	Trial Master File
TEAEs	treatment-emergent adverse event
$t_{1/2}$	half-life
ULN	upper limit of normal
US	United States
V_{ss}	apparent volume of distribution at steady state
WBC	white blood cell

10.7 Appendix 7: Protocol Amendment History

10.7.1 Amendment 2

The Protocol Amendment Summary of Changes Table for the current amendment is located directly before the Table of Contents (TOC).

10.7.2 Amendment 1

Amendment 1 (22 OCT 2020)

Overall Rationale for the Amendment:

Section Number and Name	Description of Change	Brief Rationale
Section 1, Protocol Summary Section 2.1, Study Rationale Section 3, Objectives and Endpoints Section 4.1, Overall Design Section 4.3, Justification for Dose Section 5.1, Inclusion Criteria Section 5.2, Exclusion Criteria Section 6.1, Study Intervention Administered	Addition of previously untreated patients (PUPs) and minimally treated patients (MTPs) to the study such that the study has 2 parts (Part A for previously treated patients and Part B for PUPs/MTPs)	Fulfillment of post approval commitment received from the China Center for Drug Evaluation (CDE) and China National Medical Products Administration (NMPA) to obtain additional efficacy and safety data for KOVALTRY in previously untreated/minimally treated Chinese hemophilia A patients
Section 1, Protocol Summary Section 4.4, End of Study Definition Section 6.1, Study Intervention Administered Section 6.8.3, Participant Discontinuation/Withdrawal from the Study Section 7.3.1, Treatment Logs/Bleeding Verification	Addition of a new section to describe optional immune tolerance induction therapy for participants who develop high-titer FVIII inhibitor	To provide management options to participants who develop high titer FVIII inhibitor

Section 10.5, Appendix 5: Optional Immune Tolerance Induction Treatment		
Section 8.4.1, Time Period and Frequency for Collecting AE and SAE Information	Change in the CRF location of documentation of AEs from Medical History section to AE Report Form	Correction regarding reporting process for adverse events

In addition, editorial and administrative changes have been made throughout the document.

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12. Attachments – Package Insert for China

Approval date: 18 July 2018
Revision date:

Recombinant Coagulation Factor VIII for Injection

Please carefully read the Instructions and use under the supervision of a physician

[Drug Names]

Chinese INN: Recombinant Coagulation Factor VIII for Injection

Trade name: Kovaltry® (Ke Yue Qi®)

English name: Recombinant Coagulation Factor VIII for Injection

Chinese Pinyin: Zhusheyong Chongzu Ren Ningxue Yinzi VIII

[Composition]

KOVALTRY is a sterile, stable, purified, non-pyrogenic dried concentrate produced by a genetically engineered Baby Hamster Kidney (BHK) cell line into which the human Factor VIII gene was introduced together with the human heat shock protein 70 (HSP 70) gene.

Active ingredient: Recombinant coagulation factor VIII.

Excipients: glycine, sucrose, sodium chloride, calcium chloride, histidine and polysorbate80.

[Description]

White to slightly yellow powder. Colorless and clear liquid after reconstitution by adding sterile water for injection according to the labeled amount.

[Indications]

KOVALTRY, indicated for use in adults and children with hemophilia A (congenital Factor VIII deficiency) for:

- Routine prophylaxis to reduce the frequency of bleeding episodes
- On-demand treatment and control of bleeding episodes
- Perioperative management of bleeding

KOVALTRY is not indicated for the treatment of von Willebrand disease.

[Strength]

250 IU/vial, 500 IU/vial, 1000 IU/vial

[Dosage and Administration]

For intravenous use after reconstitution only.

The dosage of children < 12 years of age is determined according to global pivotal study. The clinical data of Chinese children < 12 years of age have not been collected.

Dose

- Dosage and duration of treatment depend on the severity of the Factor VIII deficiency, the location and extent of bleeding, and the patient's clinical condition. Careful control of replacement therapy is especially important in cases of major surgery or life-threatening bleeding episodes.
- Each vial label of KOVALTRY states the Factor VIII potency in international units (IU). One IU is defined by the current WHO (World Health Organization) international standard (IS) for Factor VIII concentrate.
- Potency assignment for KOVALTRY is determined using a chromogenic substrate assay. A field study involving 41 clinical laboratories from around the world measured recoveries of KOVALTRY spiked into hemophilic plasma. The results of the field study indicated that the Factor VIII activity of KOVALTRY can be accurately measured in plasma using either a one-stage clotting or chromogenic substrate assay according to routine methods of the testing laboratory.
- The required dose for a desired Factor VIII level expressed as IU/dL (or % of normal) can be estimated using the following formula:

  Required dose (IU)
  = body weight (kg) x desired Factor VIII rise (% of normal or IU/dL)
  x reciprocal of expected/observed recovery (e.g., 0.5 for a recovery of 2 IU/dL per IU/kg)
- The expected in vivo peak increase of Factor VIII level expressed as IU/dL (or % of normal) can be estimated using the following formula:

  Estimated increment of Factor VIII (IU/dL or % of normal)
  = [Total dose (IU)/body weight (kg)] x 2 (IU/dL per IU/kg)

Examples (assuming patient's baseline Factor VIII is <1%):
(1). A peak of 50% is required in a 20 kg child. In this situation, the required dose of KOVALTRY would be 20 kg x 50 IU/dL x 0.5 (for recovery of 2 IU/dL per IU/kg) = 500 IU
(2). A dose of 2000 IU of KOVALTRY administered to a 50 kg patient should be expected to result in post-infusion Factor VIII increase of 2000 IU / 50 kg (body weight) x 2 IU/dL per IU/kg = 80 IU/dL (80% of normal)

- Adjust dose to the patient's clinical response. Patients may vary in their pharmacokinetic (e.g., half-life, incremental recovery) and clinical responses to KOVALTRY.

❖ **On-demand Treatment and Control of Bleeding Episodes**

A guide for dosing KOVALTRY for the on-demand treatment and control of bleeding episodes is provided in Table 1. The goal of treatment is to maintain a plasma Factor VIII activity level at or above the plasma levels (in % of normal or in IU/dL) outlined in Table 1.

Table 1: Dosing for Control of Bleeding Episodes

Degree of Bleeding	Factor VIII Level Required (IU/dL or % of normal)	Frequency of Doses (hours)	Duration of Therapy (days)
Minor (Early hemarthrosis, minor muscle, oral bleeds)	20–40	Repeat every 12–24 hours	At least 1 day, until bleeding episode as indicated by pain is resolved or healing is achieved
Moderate (More extensive hemarthrosis, muscle bleeding, or hematoma)	30–60	Repeat every 12–24 hours	3 to 4 days or more until pain and acute disability are resolved
Major (intracranial, intra-abdominal or intrathoracic hemorrhages, gastrointestinal bleeding, central nervous system bleeding, bleeding in the retropharyngeal or retroperitoneal spaces, or iliopsoas sheath, life or limb threatening hemorrhage)	60–100	Repeat every 8–24 hours	Until bleeding is resolved

❖ **Perioperative Management of Bleeding**

A guide for dosing KOVALTRY during surgery (perioperative management) is provided in Table 2. The goal of treatment is to maintain a plasma Factor VIII activity level at or above the plasma level (in % of normal or in IU/dL) outlined in Table 2. During major surgery, monitoring with appropriate laboratory tests, including serial Factor VIII activity assays, is highly recommended **(See [Precautions])**

Table 2: Dosing for Perioperative Management

Type of Surgery	Factor VIII Level Required (IU/dL or % of normal)	Frequency of Doses (hours)	Duration of Therapy (days)
Minor (Such as tooth extraction)	30–60 (pre- and postoperative)	Repeat every 24 hours	At least 1 day until healing is achieved
Major (Such as intracranial, intraabdominal, intrathoracic, or joint replacement surgery)	80–100 (pre- and postoperative)	Repeat every 8–24 hours	Until adequate wound healing is complete, then continue therapy for at least another 7 days to maintain Factor VIII activity of 30–60% (IU/dL)

❖ **Routine Prophylaxis**

- Individualize the patient's dose based on clinical response.
- Adults and adolescents: 20 to 40 IU of KOVALTRY per kg of body weight two or three times per week.

- Children ≤12 years old: 25 to 50 IU of KOVALTRY per kg body weight twice weekly, three times weekly, or every other day according to individual requirements. (**See [Pediatric Use]**)

1. <u>Preparation and Reconstitution before Administration</u> (refer to the Appendix in the end of the PI)

2. <u>Administration</u>
For intravenous use only.

- Inspect reconstituted KOVALTRY visually for particulate matter and discoloration prior to administration. Do not use if you notice any particulate matter or discoloration and immediately contact Bayer Medical Communications at Bayer Hotline (400-810-0360).
- Administer reconstituted KOVALTRY as soon as possible. If not, store at room temperature for no longer than 3 hours.
- Infuse KOVALTRY intravenously over a period of 1 to 15 minutes. Adapt the rate of administration to the response of each individual patient.

[Adverse Reactions]

The most frequently reported adverse reactions in clinical trials (≥3%) were headache, pyrexia, and pruritus (see Table 3).

1. Clinical Trials Experience
The safety profile of KOVALTRY was evaluated in 193 previously treated patients (PTPs) (inclusive of 51 pediatric patients <12 years of age) with at least three months of exposure to KOVALTRY. The safety analysis was done using a pooled database from three multi-center, prospective, open-label clinical studies. The median time on study for patients ≥12 years of age was 372 days with a median of 159 exposure days (EDs). The median time on study for patients <12 years of age was 182 days with a median of 73 EDs. Subjects who received KOVALTRY for perioperative management (n=5) with treatment period of 2 to 3 weeks and those who received single doses of KOVALTRY for PK studies (n=6) were excluded from safety analysis. Table 3 lists the adverse reactions reported during clinical studies. The frequency, type, and severity of adverse reactions in children are similar to those in adults.

Table 3: Adverse Reactions in Previously Treated Patients (PTPs) (N=193)

MedDRA Primary System Organ Class Preferred term	**Frequency** **N (%)**
Blood and the Lymphatic System Disorders	
Lymphadenopathy	2 (1.0%)
Cardiac Disorders	
Palpitation	2 (1.0%)
Sinus tachycardia	2 (1.0%)
Gastrointestinal Disorders	
Abdominal pain	4 (2.1%)
Abdominal discomfort	3 (1.6%)
Dyspepsia	4 (2.1%)
General Disorders and Administration Site Conditions	
Pyrexia	8 (4.1%)
Chest discomfort	2 (1.0%)
Injection site reactions[a]	5 (2.6%)
Immune System Disorders	
Hypersensitivity	1 (0.5%)

Nervous System Disorders	
Dizziness	2 (1.0%)
Dysgeusia	1 (0.5%)
Headache	14 (7.3%)
Psychiatric Disorders	
Insomnia	5 (2.6%)
Skin and Subcutaneous Tissue Disorders	
Dermatitis allergic	2 (1.0%)
Pruritus	6 (3.1%)
Rash[b]	5 (2.6%)
Urticaria	1 (0.5%)
Vascular disorders	
Flushing	1 (0.5%)

[a]Includes injection site extravasation and hematoma, infusion site pain, pruritus, and swelling
[b]Includes rash, rash erythematous, and rash pruritic

Immunogenicity

All clinical trial subjects were monitored for neutralizing antibodies (inhibitors) to Factor VIII by the modified Bethesda assay using blood samples obtained prior to the first infusion of KOVALTRY, at defined intervals during the studies and at the completion visit.

Clinical trials (Phases 1 through 3) with KOVALTRY evaluated a total of 204 pediatric and adult patients diagnosed with severe hemophilia A (Factor VIII <1%) with previous exposure to Factor VIII concentrates ≥50 EDs, and no history of inhibitors.

In the completed studies, no PTP developed neutralizing antibodies to Factor VIII. In an ongoing extension study, a 13 year old PTP had a titer of 0.6 BU after 550 EDs concurrent with an acute infection and positive IgG anticardiolipin antibodies. The Factor VIII recovery was 2.2 IU/dL per IU/kg, annualized bleeding rate (ABR) was zero, and no change in therapy was required.

In an actively enrolling clinical trial in PUPs, 6 of 14 treated subjects (42.9% with a 95% Confidence Interval of 17.7-71.1%) developed an inhibitor. Of these, 3 subjects (21.4%) had high titer inhibitors, and 3 subjects (21.4%) had transient low titer inhibitors for which no change in therapy was required.

The detection of antibody formation is dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, it may be misleading to compare the incidence of antibodies to KOVALTRY with the incidence of antibodies to other products.

[Contraindications]

KOVALTRY is contraindicated in patients who have a history of hypersensitivity reactions to the active substance, to any of the excipients, or to mouse or hamster proteins. **(See [Composition])**

[Precautions]

1 Hypersensitivity Reactions

Hypersensitivity reactions, including anaphylaxis, are possible with KOVALTRY. Early signs of hypersensitivity reactions, which can progress to anaphylaxis, may include chest or throat tightness, dizziness, mild hypotension and nausea. Discontinue KOVALTRY if symptoms (instances of severe anaphylaxis) occur and seek immediate emergency treatment.

KOVALTRY may contain trace amounts of mouse and hamster proteins **(See [Composition]).** Patients treated with this product may develop hypersensitivity to these non-human mammalian proteins.

2 Neutralizing Antibodies
Neutralizing antibody (inhibitor) formation can occur following administration of KOVALTRY. Previously untreated patients (PUPs) are at greatest risk for inhibitor development with all Factor VIII products **(see [Adverse Reactions]).**
Carefully monitor patients for the development of Factor VIII inhibitors, using appropriate clinical observations and laboratory tests. If expected plasma Factor VIII activity levels are not attained or if bleeding is not controlled as expected with administered dose, suspect the presence of an inhibitor (neutralizing antibody) .

3 Cardiovascular Risk Factors
Hemophilic patients with cardiovascular risk factors or diseases may be at the same risk to develop cardiovascular events as non-hemophilic patients when clotting has been normalized by treatment with Factor VIII.

4 Catheter-related Infections
Catheter-related infections may be observed when KOVALTRY is administered via central venous access devices (CVADs). These infections have not been associated with the product itself.

5 Monitoring Laboratory Tests
- Monitor plasma Factor VIII activity levels using a validated test to confirm that adequate Factor VIII levels have been achieved and maintained (**see [Dosage and Administration]**).
- Monitor for development of Factor VIII inhibitors. Perform a Bethesda inhibitor assay if expected Factor VIII plasma levels are not attained or if bleeding is not controlled with the expected dose of KOVALTRY. Use Bethesda Units (BU) to report inhibitor titers.

[Use in Pregnancy and Lactation]

1. Pregnancy

Risk Summary
There are no data with KOVALTRY use in pregnant women to inform on drug-associated risk. Animal reproduction studies have not been conducted using KOVALTRY. It is not known whether KOVALTRY can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. KOVALTRY should be given to a pregnant woman only if clearly needed. The rates for birth defects and miscarriage based on available general population worldwide are 2.6-6.9% and 10-21%, respectively.

2. Lactation
Risk Summary
There is no information regarding the presence of KOVALTRY in human milk, the effects on the breastfed infant, or the effects on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for KOVALTRY and any potential adverse effects on the breastfed infant from KOVALTRY or from the underlying maternal condition.

[Pediatric Use]

The dosage of children < 12 years of age is determined according to global pivotal study. The clinical data of Chinese children < 12 years of age have not been collected.
Safety and efficacy studies with KOVALTRY have been performed in pediatric PTPs. Body weight adjusted clearance of Factor VIII in children ≤12 years of age is higher than in adults and adolescents. Consider higher or more frequent dosing in children to account for this difference in clearance **(see [Pharmacology and toxicology]).**

[Geriatric Use]

Clinical studies with KOVALTRY did not include patients aged 65 and over to determine whether or not they respond differently from younger patients. However, clinical experience with other Factor VIII products has not identified differences between the elderly and younger patients. As with any patient receiving recombinant Factor VIII, dose selection for an elderly patient should be individualized.

[Drug interactions]

No interactions of human coagulation factor VIII products with other medicinal products have been reported.

[Overdose]

No symptoms of overdose have been reported.

[Clinical Studies]

The safety and efficacy of KOVALTRY for on-demand treatment and control of bleeding episodes, perioperative management of bleeding, and routine prophylaxis in subjects with severe hemophilia A (<1% Factor VIII) was evaluated in three international (including China.) clinical studies. Immunocompetent subjects with severe hemophilia A (Factor VIII activity ≤1%) and no history of Factor VIII inhibitors were eligible for the trials.

Study 1: a multi-center, open-label, cross-over, uncontrolled, study in adolescent and adult (age ≥12 years to <65 years) PTPs (≥150 EDs) evaluated the pharmacokinetics, efficacy and safety of routine prophylaxis, and perioperative management of bleeding of KOVALTRY (see Table 4). The primary efficacy variable was ABR. The prophylactic regimen was 20 to 50 IU/kg two or three times per week in which the dosing frequency was assigned by the investigator based on the subject's individual requirements.

Study 2: a multi-center, open-label, cross-over, uncontrolled, randomized study in adolescent and adult (age ≥12 years to <65 years) PTPs (≥150 EDs) evaluated the superiority of prophylaxis over on-demand treatment with KOVALTRY over a 12 one-year treatment period (see Table 4). The primary efficacy variable was ABR. The prophylactic regimen was 20 to 30 IU/kg two times per week or 30 to 40 IU/kg three times per week and the treatment group was assigned by randomization.

Study 3: a multi-center, open-label, uncontrolled study in pediatric (age ≤12 years) PTPs (≥50 EDs) evaluated the pharmacokinetics, efficacy and safety of routine prophylaxis, and perioperative management of bleeding of KOVALTRY (see Table 5). The primary efficacy variable was annualized number of total bleeds during routine prophylaxis that occurred within 48 hours following previous prophylaxis infusion. ABR during prophylaxis, independent of time of infusion, was also analyzed. The prophylactic regimen was 25 to 50 IU/kg at frequencies of either 2 times per week, 3 times per week or every other day and could be adapted to individual subject's need by the investigator.

In all studies, treatments of breakthrough bleeds and perioperative management were at the investigator's discretion based on standard of care.

A total of 204 subjects were enrolled in the completed clinical trials, 153 subjects ≥12 years of age and 51 subjects <12 years of age. One hundred-forty (140) subjects were treated for at least 12 months, and 43 of these subjects were treated for 24 months.

Table 4: Overview of Study 1 (Prophylaxis Treatment Phase) and Study 2

	Study 1(N=62)	**Study 2(N=80)**
Age: mean ±SD	31.5±12.7 years	29.6 ±11.0 years
Previous treatment: %	Prophylaxis: 80.6%	On-demand: 100%
Number of Target joints at baseline: mean ±SD	1.4 ±1.3	3.0 ±2.1
Joint hemorrhage history (during 12 months prior to study): mean ±SD of joint bleeds	8.0 ±11.9	32.1 ± 23.8

Table 5: Overview of Study 3

	Study 3	
	Previously Treated Patients (PTPs) 0 to <6 yrs (N=25)	**Previously Treated Patients (PTPs) 6 to 12 yrs (N=26)**
Age: mean ±SD (range)	3.8 ±1.3 years (1-5)	8.8 ±1.8 years (6-11)
Previous treatment: %	Prophylaxis: 92.0%	Prophylaxis: 65.4%
Number of Target joints at baseline: mean ± SD	0.2 ±0.4	0.7 ±1.1

❖ **On-demand Treatment and Control of Bleeding Episodes**

Adolescents and Adults

A total of 1892 bleeding episodes in 110 subjects were treated with KOVALTRY in Study 1 and Study 2 (see Table 6). The majority of the bleeding episodes were spontaneous, localized in joints, and mild to moderate in severity.

In Study 1 and Study 2, the treatment responses in a total of 1859 treated bleeds were assessed by the subjects compared to their previous treatment experience.

Table 6: On-demand Treatment and Control of Bleeding Episodes in Adolescents and Adults Treated with KOVALTRY

Characteristics of Bleeding Episodes	Study 1		Study 2	
	Prophylaxis Main Study N=62	Prophylaxis Extension N=55	Prophylaxis N=59	On-demand N=21
Total number of bleeds	241	154	293	1204
Spontaneous: n/total (%)	153/241 (63.5%)	79/150[a] (52.7%)	209/283[a] (73.9%)	943/1202[a] (78.5%)
Trauma: n/total (%)	79/241 (32.8%)	70/150[a] (46.7%)	74/283[a] (26.1%)	258/1202[a] (21.5%)
Joint bleeds: n/total (%)	191/241 (79.3%)	120/154 (77.9%)	255/293 (87.0%)	924/1197[a] (77.2%)
Mild/moderate: n/total (%)	215/241 (89.2%)	130/153[a] (84.9%)	260/293 (88.8%)	1092/1196[a] (91.3%)
% of bleeds treated with ≤2 infusions	87.0%		96.2%	95.3%
Response to treatment of bleeds assessed as "Excellent" or "Good": n/total[b] (%)	190/235 (80.9%)	107/149 (71.8%)	172/279 (61.6%)	834/1196 (69.7%)
Median dose per infusion (range)	31.6 IU/kg (14–67 IU/kg)		29.4 IU/kg (19–49 IU/kg)	22.0 IU/kg (11–35 IU/kg)

[a]Total number excluding uncharacterized bleeds
[b]The % is calculated from number of treated bleeds assessed for response

Children 12 Years of Age and Younger

A total of 97 bleeding episodes in 28 pediatric subjects were treated with KOVALTRY. Majority (96.9%) of the bleeds were mild to moderate in severity. Fifty-nine (72.8%) bleeds were trauma related. During the 6 month treatment period, the median dose of KOVALTRY for the treatment of breakthrough bleeds was 36.94 IU/kg per infusion (range 20.8– 71.6 IU/kg).

Assessment of response to treatment of bleeds was as follows:

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: No improvement at all between infusions or condition worsens.

The hemostatic efficacy in on-demand treatment of bleeds was assessed as either "good" or "excellent" in 90.1% of cases (97.8% in the younger age group and 81.0% in the older age group). Majority of bleeds (89.7%) were successfully treated with ≤2 infusions. Response to treatment was similar for children aged 0 to <6 compared to 6 to 12 years of age (see Table 7).

Table 7: On-demand Treatment and Control of Bleeding Episodes in Children Treated with KOVALTRY

Characteristics of Bleeding Episodes	Study 3		
	PTPs 0 to <6 yrs (N=25)	PTPs 6 to 12 yrs (N=26)	PTPs 0 to 12 yrs (N=51)
Total number of bleeds	52	45	97
Spontaneous: n/total (%)	8/44[a] (18.2%)	12/37[a] (32.4%)	20/81[a] (24.7%)
Trauma: n/total (%)	36/44[a] (81.8%)	23/37[a] (62.2%)	59/81[a] (72.8%)
Joint bleeds: n/total (%)	10/52 (19.2%)	22/45 (48.9%)	32/97 (33.0%)
Mild/moderate: n/total (%)	50/52 (96.2%)	44/45 (97.8%)	94/97 (96.9%)
% bleeds treated with ≤2 infusions	92.4%	86.7%	89.7%
Response to treatment of bleeds assessed as "Excellent" or "Good": n/total[b] (%)	43/44 (97.8%)	30/37 (81.0%)	73/81 (90.1%)
Median dose per infusion (range)	38.7 IU/kg (20.8–71.6 IU/kg)	32.4 IU/kg (21.7–50.0 IU/kg)	36.9 IU/kg (20.8–71.6 IU/kg)

[a]Total number of treated bleeds
[b]The % is calculated from number of treated bleeds assessed for response

❖ **Perioperative Management**

A total of 14 major and 46 minor surgeries were performed in 44 previously treated subjects (43 adults and adolescents and 1 child under 12 years of age) with severe hemophilia A. Seven of the 14 major surgeries were orthopedic procedures, including joint replacement. Approximately 51% of the minor surgeries were dental extractions. All subjects received KOVALTRY as bolus infusions. In the adolescent and adult subjects, the initial KOVALTRY doses administered ranged between 3000–5000 IU. The median total dose on the day of surgery was 107.5 IU/kg (range 60–207 IU/kg). In a single subject younger than 12 years of age who underwent a major surgery, the total initial KOVALTRY dose administered was 2500 IU (108.7 IU/kg).

The blood loss, during and after surgery, was within expected ranges. Hemostatic control was assessed by surgeons as "good" (perioperative bleeding slightly but not clinically significantly increased over expectations for the non-hemophilic patient; treatment similar to non-hemophilic patient) or "excellent" (perioperative blood loss similar to the non-hemophilic patient).

❖ **Routine Prophylaxis**

Adolescents and Adults

A total of 140 subjects were treated with KOVALTRY for at least 12 months with median (range) 157 EDs (25-178) in Study 1, [305 EDs (25-355) inclusive of extension phase], and 153 EDs (103-187) in Study 2 (see Table 8). In both studies, subjects in the Intent-to-Treat (ITT) population received 95% to 100% of the prescribed number of prophylaxis infusions.

Table 8: Prophylaxis Treatment with KOVALTRY in Adolescents and Adults – Treatment Exposure

	Study 1 (N=62)[a]	**Study 2 (N=59)**
Median nominal [b] prophylaxis dose/ infusion (range) All Prophylaxis 2 times per week Prophylaxis 3 times per week	 31.2 IU/kg (21-43 IU/kg) 35.0 IU/kg (21-42 IU/kg) 31.1 IU/kg (24-43 IU/kg)	 31.7 IU/kg (21-42 IU/kg) 30.4 IU/kg (21-34 IU/kg) 37.4 IU/kg (30-42 IU/kg)
Treatment duration	1 year main study	1 year

Study 1: 2 times per week (n=18); 3 times per week (n=44)
Study 2: 2 times per week (n=28); 3 times per week (n=31)
[a]Study 1 included PK, safety and efficacy of prophylaxis and hemostasis during surgeries. Prophylaxis phase data are presented.
[b] nominal dose is based on the labelled potency

The mean and median ABR for the ITT population in Study 1 was 3.8 ± 5.2 and 1 bleed/year, respectively. In Study 2, comparison of the bleeding rates between subjects receiving on-demand therapy versus prophylaxis in an ANOVA demonstrated a statistically significant difference ($p<0.0001$) in the median ABR in subjects receiving on-demand therapy (60 bleeds per year) as compared to subjects receiving prophylaxis (2 bleeds per year). In Study 2, mean ABR in subjects receiving on-demand therapy was 57.7 ± 24.6 versus 4.9 ± 6.8 in the subjects receiving prophylaxis.

Table 9: ABR in Adolescent and Adult Subjects

	Study 1 (N=62)		**Study 2 (N=59)**	
	2 times per week (n=18)	**3 times per week (n=44)**	**2 times per week (n=28)**	**3 times per week (n=31)**
ABR Median (IQR[a] Q1; Q3)				
All Bleeds	1.0 (0.0; 8.0)	2.0 (0.5; 5.0)	4.0 (0.0; 8.0) Month 1-6[b]: 4.1; Month 7-12[b]: 1.1	2.0 (0.0; 4.9) Month 1-6[b]: 2.0; Month 7-12[b]: 2.0
Spontaneous Bleeds	0.5 (0.0; 2.0)	1.0 (0.0; 3.9)	2.0 (0.0; 6.5)	0.0 (0.0; 3.0)
Joint Bleeds	0.5 (0.0; 7.0)	1.8 (0.0; 3.0)	2.5 (0.0; 7.5)	1.0 (0.0; 4.0)
Subjects with Zero Bleeding Episodes[c] % (n)	37.5% (6/16[d])	62.5% (10/16[d])	28.6% (8/28[e])	25.8% (8/31[e])

[a]IQR = Interquartile Range
[b]Month 1-6 refers to the first six months of the treatment period and Month 7-12 refer to the second six months of the treatment period
[c]Observation of one-year treatment period
[d]n=total number of subjects with zero bleeds
[e]n=total number of subjects randomized to treatment arms

The ABR for subjects (n=21) receiving on-demand therapy in Study 2 [median (IQR Q1; Q3)] for all bleeds: 60 (41.7; 76.3); spontaneous bleeds: 42.1 (24.3; 61.3); joint bleeds: 38.8 (24.3; 60.0).

Children 12 Years of Age and Younger
A total of 51 PTPs were treated with KOVALTRY for at least 6 months with median (range) 73 EDs (37-103) (see Table 10). Subjects received >95% of the prescribed number of prophylaxis infusions.

Table 10: Prophylaxis Treatment with KOVALTRY in Children 12 Years of Age or Younger – Treatment Exposure

	Study 3	
	PTPs 0 to <6 yrs (N=25)	**PTPs 6 to 12 yrs (N=26)**
Treatment regimen[a] during study (6 months) n (%)		
2 times per week	9 (36%)	13 (50%)
3 times per week or every other day	16 (64%)	13 (50%)
Nominal prophylaxis dose per infusion, median (range)	36.4 IU/kg (21–58 IU/kg)	31.8 IU/kg (22–50 IU/kg)

[a]Treatment regimen at the start of the study. Study duration was six months.

In children 12 years of age and younger (n=51), the median (IQR Q1; Q3) ABR within 48 hours after prophylactic infusion was 0 (0; 4) for all bleeds, and 0 (0; 0) for spontaneous and joint bleeds. The median (IQR Q1; Q3) ABR during prophylactic treatment independent of time of infusion was 1.9 (0; 6) for all bleeds, 0 (0; 0) for spontaneous bleeds and 0 (0; 2) for joint bleeds. The mean ABR within 48 hours after prophylactic infusion was 2.04 ± 2.91. The mean ABR at any time during the prophylaxis regimen was 3.75 ± 4.98.

In both age groups (0 to <6 years and 6 to 12 years), the ABR for spontaneous bleeds and joint bleeds within 48 hours after prophylactic treatment [ABR median (IQR Q1; Q3)] was 0 (0; 0). The median (IQR Q1; Q3) annualized number of spontaneous bleeds during prophylactic treatment independent of time of infusion was 0 (0; 0). The median (IQR Q1; Q3) annualized number of joint bleeds during prophylactic treatment independent of time of infusion was 0 (0; 1.9) in 0 to <6 years age group and 0 (0; 2.1) in 6 to 12 years age group (see Table 11).

The majority (32/53) of bleeds that occurred within 48 hours after a previous prophylaxis infusion were trauma related. Twenty-three (45.1%) subjects reported no bleeds during the six-month prophylaxis period.

Table 11: ABR in Children 12 Years of Age or Younger

	Study 3			
	PTPs 0 to <6 yrs (N=25)		**PTPs 6 to 12 yrs (N=26)**	
	Within 48 hrs after prophylactic treatment	During prophylactic treatment[b]	Within 48 hrs after prophylactic treatment	During prophylactic treatment[b]
All Bleeds ABR Median (IQR[a] Q1; Q3)	1.9 (0.0; 4.0)	2.0 (0.0; 6.0)	0.0 (0.0; 2.0)	0.9 (0.0; 5.8)
Number of Subjects with Zero Bleeding Episodes (%)	10 (40%)		13 (50%)	

[a]IQR = Interquartile Range
[b]Independent of time of infusion

<Chinese patients clinical study summary>

There were twenty-three subjects in China entering study 2, which was randomized and received at least 1 injection of BAY 81-8973. No relevant differences between the on-demand and prophylaxis groups were seen for demographic and disease characteristics at baseline.

Table 12: Chinese subgroup overview

	China subgroup（N = 23）
Age: mean±SD	28.6 ± 8.8years*
Previous treatment: %	On-demand：100%
Number of Target joints at baseline: mean±SD	2.5 ± 1.8
Joint hemorrhage history (during 12 months prior to study): mean±SD of joint bleeds	38.1 ± 26.5

*The only adolescent subject in the Chinese subset was randomized to high-dose prophylaxis.

❖ **On-demand Treatment and Control of Bleeding Episodes**

A total of 499 bleeds were reported in the 23 Chinese subjects during this study. Most of these bleeds were of mild or moderate intensity and were spontaneous bleeds into joints.

Table 13：On-demand Treatment and Control of Bleeding Episodes in China Subgroup Patients Treated with KOVALTRY

Characteristics of Bleeding Episodes	**China subgroup**	
	prophylaxis N = 17	**On-demand N = 6**
Total number of bleeds	67	432
Spontaneous: n/total (%)	46/62[a]（74.2%）	299/430[a]（69.5%）
Trauma: n/total (%)	16/62[a]（25.8%）	131/430[a]（30.5%）
Joint bleeds: n/total (%)	56/67（83.6%）	314/432（72.7%）
Mild/moderate: n/total (%)	62/67（92.5%）	420/432（97.2%）
% of bleeds treated with ≤2 infusions	97.0%	97.7%
Response to treatment of bleeds assessed as “Excellent” or “Good”: n/total (%)	39/62[b]（62.9%）	237/432（54.9%）
Median dose per infusion (range)	27.33 IU/kg（23.5-41.6 IU/kg）	21.39 IU/kg（15-23.5 IU/kg）

[a] Total number excluding uncharacterized bleeds.
b: 5 missing data of response to treatment of bleeds in prophylaxis group.

❖ **Perioperative Management**

A total of 1 major and 7 minor surgeries were performed in 4 previously treated subjects with severe hemophilia A. 1 major surgery was elective hemorrhoidectomy with local anesthesia. 6 of 7 minor surgeries were dental extractions. The remaining surgery was an oral pseudotumor resection. All subjects received KOVALTRY as bolus infusions. The initial KOVALTRY doses administered of the major surgery was 3252 IU (pre-surgery) and 3252 IU in the same day (post-surgery). The pre-surgery doses for 7 minor surgeries ranged from 1500 to 2033 IU.

The blood loss, during and after surgery, was within expected ranges. Hemostatic control was assessed by surgeons as ”good” (perioperative bleeding slightly but not clinically significantly increased over expectations for the non-hemophilic patient; treatment similar to non-hemophilic patient) or “excellent” (perioperative blood loss similar to the non-hemophilic patient).

❖ **Routine Prophylaxis**

A total of 17 subjects were treated with KOVALTRY for at least 12 months with median (range) 153 EDs (106-182).

Table 14: Prophylaxis Treatment with KOVALTRY in Adolescents and Adults – Treatment Exposure

	China subgroup (N = 17[a])
Median nominal prophylaxis dose/ infusion (range)	
All	31.69 IU/kg（21.5-41.9 IU/kg）
Prophylaxis, 2 times per week, low dose	30.42 IU/kg（21.6-32.0 IU/kg）
Prophylaxis, 3 times per week, high dose	40.41 IU/kg（30.7-41.9 IU/kg）
Treatment duration	1 year

a: 2 times per week (n=7); 3 times per week (n=10)

Comparison of the bleeding rates between subjects receiving on-demand therapy versus prophylaxis in an ANOVA demonstrated a statistically significant difference ($p<0.0001$) in the median ABR in subjects receiving on-demand therapy (63.54 bleeds per year) as compared to subjects receiving prophylaxis (1.98 bleeds per year). Mean ABR in subjects receiving on-demand therapy was 71.93 ± 22.96 versus 3.91 ± 4.79 in the subjects receiving prophylaxis.

Table 15：ABR in Adolescent and Adult Subjects

	China subgroup prophylaxis（N = 17）	
	2 times per week（n=7）	**3 times per week（n=10）**
ABR Median (IQR[a] Q1; Q3)		
All Bleeds	5.04（1.95；11.04） 1-6 months [b]：4.02； 7-12months [b]：3.64	1.98（0.0；2.0） 1-6 months [b]：1.93； 7-12 months [b]：1.95
Spontaneous Bleeds	2.01（0.0；9.0）	0.0（0.0；0.0）
Joint Bleeds	4.03（2.0；7.9）	0.0（0.0；2.0）
Subjects with Zero Bleeding Episodes[c] % (n)	14.3% (1/7 [d])	30.0% (3/10[d])

[a]IQR = Interquartile Range
[b]Month 1-6 refers to the first six months of the treatment period and Month 7-12 refer to the second six months of the treatment period
[c]Observation of one-year treatment period
[d]n=total number of subjects randomized to treatment arms

[Pharmacology and toxicology]

Pharmacology

KOVALTRY temporarily replaces the missing clotting Factor VIII.
Plasma clotting time as measured by the activated partial thromboplastin time (aPTT) is prolonged in patients with hemophilia A. Treatment with KOVALTRY normalizes the aPTT.

Toxicology

KOVALTRY was negative in the modified *in-vitro* (Mammalian Mutation and Chromosome Aberration Assay with Mouse Lymphoma Cells) genotoxicity test.
Studies in animals to evaluate carcinogenic potential of KOVALTRY have not been performed.

[Pharmacokinetics]

The pharmacokinetics (PK) of KOVALTRY were investigated in PTPs (0 to 61 years of age) with severe Hemophilia A following administration of 50 IU/kg of KOVALTRY. The PK parameters of KOVALTRY are presented in Table 16 (one-stage clotting assay) and Table 17 (chromogenic substrate assay). The PK of KOVALTRY were similar between single and repeat dosing (in 19 subjects following 6 to 12 months of prophylaxis).

Table 16: Pharmacokinetic Parameters [Arithmetic Mean ±SD] for KOVALTRY (50 IU/kg dose), One-Stage Clotting Assay

Parameter [unit]	12 to 17 yrs (N=5)	≥18 yrs (N=21)
AUC [IU*h/dL]	1013.9 ± 286.8	1601.3 ± 520.0
C_{max} [IU/dL]	91.7 ± 28.7	99.7 ± 14.9
$t_{½}$ [h]	11.7 ± 1.11	14.3 ± 3.7
MRT_{IV} [h]	16.1 ± 0.8	19.8 ± 5.7
V_{ss} [dL/kg]	0.85 ± 0.24	0.63 ± 0.11
CL [dL/h/kg]	0.053 ± 0.017	0.035 ± 0.012

AUC: area under the curve
C_{max}: maximum drug concentration in plasma after single dose
$t_{½}$: terminal half-life
MRT_{IV}: mean residence time after an IV administration
V_{ss}: apparent volume distribution at steady-state
CL: clearance

The PK parameters of KOVALTRY for 8 subjects in age group 0 to <6 years and 10 subjects in age group 6 to <12 years are shown in Table 17. In general, children <12 years of age demonstrated lower plasma concentrations when compared to PTP children ≥12 years of age.

Table 17: Pharmacokinetic Parameters [Arithmetic Mean ±SD] for KOVALTRY (50 IU/kg dose), Chromogenic Substrate Assay

Parameter [unit]	0 to <6 yrs (N=8)	6 to <12 yrs (N=10)[b]	12 to 17 yrs (N=5)	≥18 yrs (N=21)
AUC [IU*h/dL]	1544.7 ± 387.1[a]	1214.5 ± 395.1	1572.0 ± 448.0	2103.4 ± 702.8
C_{max} [IU/dL]	89.6 ± 27.4	81.6± 17.8	132.5 ± 46.3	133.1 ± 20.4
$t_{½}$ [h]	12.1 ± 2.7[a]	12.0 ± 2.1	14.4 ± 5.5	14.2 ± 3.5
MRT_{IV} [h]	17.7 ± 3.6[a]	17.8 ± 2.9	19.8 ± 5.8	19.9 ± 4.9
V_{ss} [dL/kg]	0.57 ± 0.13[a]	0.79 ± 0.23	0.71 ± 0.39	0.50 ± 0.11
CL [dL/h/kg]	0.033 ± 0.009[a]	0.045 ± 0.016	0.034 ± 0.010	0.027 ± 0.010

[a]n=7
[b]One subject considered PK outlier was excluded

Incremental Recovery:
Recovery values according to the chromogenic assay were similar to measurements with the one-stage assay (see Table 18). Incremental Recovery analysis after 6 months of prophylactic treatment yielded comparable results with incremental recovery after the first dose (see Table 19).

Table 18. Incremental Recovery in PTPs ≥ 12 Years of Age

	Study 1	Study 2	Pooled Analysis
Study participants	**N=59**	**N=56**	**N=115**
Chromogenic assay results Median (Q1; Q3) (IU/dL per IU/kg)	2.5 (2.1; 2.8)	2.1 (1.7; 2.4)	2.3 (1.8; 2.6)
One-stage assay results Median (Q1; Q3) (IU/dL per IU/kg)	2.2 (1.9; 2.5)	2.1 (1.7; 2.3)	2.2 (1.8; 2.4)

Table 19: Incremental Recovery in PTPs 0-12 Years of Age

	Study 3	
	PTPs 0 to <6 yrs	**PTPs 6 to 12 yrs**
Study participants	**N=24**	**N=25**
Start of study: Chromogenic assay results Median (Q1; Q3) (IU/dL per IU/kg)	1.6 (1.3; 1.9)	1.7 (1.4; 2.0)
	N=23	**N=25**
After 6 months: Chromogenic assay results Median (Q1; Q3) (IU/dL per IU/kg)	1.8 (1.4; 2.0)	1.8 (1.1; 2.1)

[Storage]

KOVALTRY should be stored and transported at 2-8℃. Do not freeze.

Administer reconstituted KOVALTRY as soon as possible. If not, store at room temperature for no longer than 3 hours.

[Package]

- Packaging materials in direct contact with drug product: Type I glass vial , bromobutyl grey stopper
- A vial of recombinant coagulation factor VIII for injection
- A prefilled diluent syringe containing 2.5 ml of sterile water for injection
- A sterile vial adapter
- A single use administration set with filter

[Shelf life]

30 months

[Executive Specification]

Registration specification for imported drug JS20160071

[Import Drug License No.]

250 IU/vial：CCI [redacted]

500 IU/vial：CCI [redacted]

1000 IU/vial：CCI [redacted]

[Manufacturer]

Name: Bayer Health Care LLC

Address: 800 Dwight Way, Berkeley, CA 94710, US

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[Hotline] 400-810-0360

<Appendix: Preparation and Reconstitution>

- Reconstitute and administer KOVALTRY with the components provided with each package. If any component of the package is opened or damaged, do not use this component.
- For any questions about the handling, reconstitution and administration of KOVALTRY, contact Bayer Medical Communications at Bayer Hotline (400-810-0360).

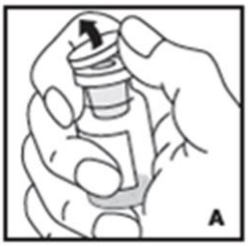
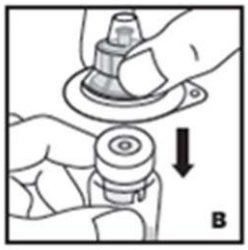
The procedures below are provided as general guidelines for the reconstitution of KOVALTRY using the sterile vial adapter with a 15 micrometer filter and a prefilled diluent syringe, which together serve as an alternative needleless reconstitution system.

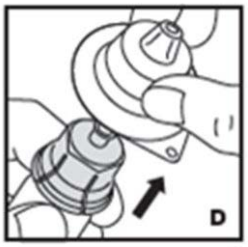
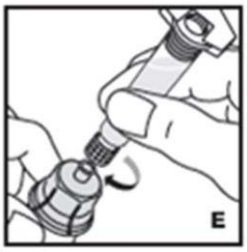
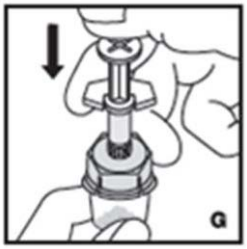
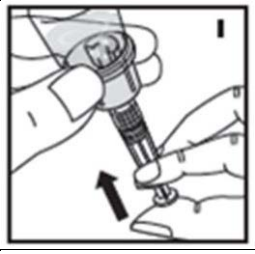
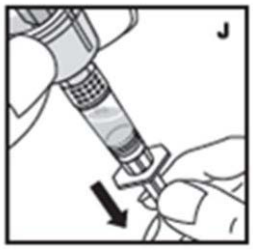
Usability Testing of Vial Adapter

Usability testing was conducted with 60 users, including 15 pediatric hemophilia A patients (between 10-17 years of age), 15 adult hemophilia A patients (≥18 years of age), 15 caregivers, and 15 healthcare providers. To mimic real life, the pediatric and adult patients and the caregivers were given minimal training, which included participants performing a supervised reconstitution and later performing a single unaided reconstitution. Healthcare providers were untrained in this study and could learn the procedure from the provided Instructions for Use. All participants were able to successfully and safely use the vial adapter device for reconstitution.

Reconstitution

- Work on a clean surface and wash hands thoroughly using soap and warm water before performing the procedures.
- Reconstitute KOVALTRY with the components provided with each package. If any component of the package is opened or damaged, do not use this component.
- Filter the reconstituted product to remove potential particulate matter in the solution. Filtering is achieved by using the vial adapter.

1.Warm both unopened KOVALTRY vial and prefilled diluent syringe in your hands to a comfortable temperature (do not exceed 37°C or 99°F).	
2. Remove the protective cap from the vial (A). Aseptically cleanse the rubber stopper with a sterile alcohol swab, being careful not to handle the rubber stopper.	
3. Place the product vial on a firm, non-skid surface. Peel off the paper cover on the vial adapter plastic housing. Do not remove the adapter from the plastic housing. Holding the adapter housing, place over the product vial and firmly press down (B). The adapter will snap over the vial cap. Do not remove the adapter housing at this step.	
4. Holding the syringe by the barrel, snap the syringe cap off the tip (C). Do not touch the syringe tip with your hand or any surface. Set the syringe aside for further use.	

5. Now remove and discard the adapter plastic housing (D).	
6. Attach the prefilled syringe to the vial adapter thread by turning clockwise (E).	
7. Remove the clear plastic plunger rod from the carton. Grasp the plunger rod by the top plate. Avoid touching the sides and threads of the plunger rod. Attach the plunger rod by turning it clockwise into the threaded rubber stopper of the prefilled syringe (F).	
8. Inject the diluent slowly by pushing down on the plunger rod (G).	
9. Swirl vial gently until all powder on all sides of the vial is dissolved (H). Do not shake vial. Be sure that all powder is completely dissolved. Do not use if solution contains visible particles or is cloudy.	
10. Push down on the plunger to push all air back into the vial. Then while holding the plunger down, turn the vial with syringe upside-down (invert) so the vial is now above the syringe (I).	
11. Withdraw all the solution into the syringe by pulling the plunger rod back slowly and smoothly (J). Tilt the vial to the side and back to make sure all the solution has been drawn toward the large opening in the rubber stopper and into the syringe. Remove as much air as possible before removing the syringe from the vial by slowly and carefully pushing the air back into the vial.	

12. Detach the syringe with plunger rod from the vial adapter by turning counter-clockwise. Attach the syringe to the administration set provided and inject intravenously (K). Note: follow instructions for infusion set provided.	

Pooling

If the dose requires more than one vial, reconstitute each vial as described above with the diluent syringe provided. Use a larger plastic syringe (not provided) to combine the content of the vials into the syringe.