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Title page

A Post Approval Commitment 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

Bayer study drug	KOVALTRY (No. BAY 81-8973)		
Study purpose:	Fulfill a post-approval commitment for KOVALTRY received from the China Center for Drug Evaluation (CDE) and China National Medical Products Administration (NMPA) to provide additional efficacy, safety and PK data for KOVALTRY in previously treated Chinese severe hemophilia A patients (PTPs), and additional efficacy and safety data in previously untreated/minimally treated Chinese patients (<6 years of age) with severe hemophilia A (PUPs/MTPs)		
Clinical study phase:	Phase IV	**Date:**	17NOV2021
Study No.:	19855	**Version:**	2.0
Author:	PPD		

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The approval of the Statistical Analysis Plan is documented in a separate Signature Document.

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Abbreviations

AE	Adverse event
CI	Confidence interval
CSR	Clinical Study Report
GCP	Good Clinical Practice
ICH	International Council for Harmonisation
MedDRA	Medical Dictionary for Regulatory Activities
N/A	Not applicable
PPS	Per-protocol set
SAE	Serious adverse event
SAP	Statistical Analysis Plan
AE	Adverse event
AUC	Area under the curve
BU	Bethesda unit
CL	clearance
C_{max}	maximum concentration
dL	deciliter
CRF	Case Report Form
eCRF	Electronic Case Report Form
ED	exposure day
EPD	Electronic Patient Diary
FVIII	Factor VIII
IU	International Unit
IVR	in vivo recovery
kg	kilogram
LLOQ	lower limit of quantification
ITT	Intent-to-treat
ITI	Immune tolerance induction
MedDRA	Medical Dictionary for Regulatory Activities
MRT	mean residence time
n/a	not applicable
PDD	Protocol Deviations Document
PPS	Per-Protocol Analysis Set
PTP	previously treated patient
PUP	previously untreated patient
QoL	quality of life
rFVIII	recombinant Factor VIII
PP	Per-protocol
SAF	Safety Analysis Set
SAP	Statistical Analysis Plan
$t_{1/2}$	half-life
TLF	Tables, Listings, Figures
V_{ss}	steady state volume

1. Introduction

This statistical analysis plan (SAP) version 2.0 is based on the finalized Protocol Version 2.0, dated 22 OCT 2020.

The protocol version 2.0, dated 22 OCT 2020 is integration of the original protocol version 1.0, dated 29 Jan 2020 and the amendment 1.

This SAP describes the study objective, study design, analysis sets, all endpoints, and statistical analysis methods. Complete details of Tables, Listing and Figures (TLFs) specifications as well as dataset details and data handling specifications will be provided in separate "TLF specifications" and "Analysis Datasets" documents as an integral part of this SAP.

2. Study Objectives

2.1 Study Objectives – Part A (PTPs)

Primary objective

- Evaluate the efficacy of prophylaxis treatment with KOVALTRY in previous treated Chinese children (<12 years) and adolescents/adults (≥ 12 years) with severe hemophilia A.

Secondary objectives

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

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.

Pharmacokinetic

- Evaluate pharmacokinetics (PK) of KOVALTRY in Chinese children (<12 years) and adolescents/adults (≥ 12 years to 65 years) severe hemophilia A patients.

2.2 Study Objectives – Part B (PUPs)

Primary objective

- Evaluate 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.

Secondary objectives

Efficacy

- Evaluate 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

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.

3. Study Design

This is a multicenter, uncontrolled open-label, two group treatment study to assess efficacy, safety and PK of KOVALTRY in previously treated Chinese children and adolescents/ adults with severe hemophilia A.

Part A (PTPs)

Part A will assesss 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 (30 children and 12 adolescents/adults). PK will be assessed in a subset of 12 children (<12 years) and in 12 adolescents/adults (≥12 years).

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 with the following dose regimen for prophylaxis 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 study visit/Early Termination). All participants will also receive a safety follow-up call approximately 2 weeks after the final study visit.

Part B (PUPs)

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 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 difrectly 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 [may be combined with the Screening visit for PUPs], 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.

3.1 Sample size determination

3.1.1 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 year 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). 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.

3.1.2 Part B (PUPs)

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 (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%.

4. General Statistical Considerations

4.1 General Principles

There is no confirmatory comparison planned for this study, study results will be numerically evaluated.

Part A and Part B will be analyzed separately, both for efficacy and safety. The optional ITI treatment period will only be considered for the safety analysis.

The efficacy and safety analysis will be presented as summary statistics by age groups (<12 or >=12 years of age) in Part A.

The statistical evaluation will be performed by using the software package SAS release 9.2 or higher (SAS Institute Inc., Cary, NC, USA). All variables will be analyzed by descriptive statistical methods. The number of data available and missing data, mean, standard deviation, minimum, quartiles, median, and maximum will be calculated for metric data. Frequency tables will be generated for categorical data.

4.2 Handling of Dropouts

Annualized number of total bleeds will be calculated for all subjects, including dropouts. Subjects who drop from the study will be included in a listing.

During the study, temporary discontinuation of study drug could happen, the duration of interruption of study intervention (i.e. prophylaxis treatment with KOVALTRY) should not be more than 2 weeks. Prolonged periods (> 2 weeks) or repeated breaks in the prophylaxis schedule should be avoided and could result in the study participant treated as drop out, or being removed from the study.

4.3 Handling of Missing Data

All missing or partial data will be presented in the subject data listing as they are recorded on the Case Report Form (CRF).

Missing or incomplete AE start and end date or time:
For the purpose of treatment emergent flags, missing AE start day will be imputed as the 15th of the month. However, if the AE start day is missing, but the AE starts during the same month as the first dose, or if the AE starts on the same day as the first dose, but the AE start time is missing, the AE start day (and time in the second case) will be taken from first dose start day (and time). If both day and month of AE start date are missing, day and month will be imputed as July 1st, or the date of the first dose, whichever comes later.

Drug-related AE tables will include AEs with missing values of causality.

Missing or incomplete concomitant medication start and end date or time:
When computing concomitant medication start dates, if day is missing, it will be imputed as the 15th of the month . If month and day are missing, it will be imputed as 1 July. If necessary, adjust imputed dates so they are not before the birth date.

Other missing data will not be imputed.

4.4 Interim Analyses and Data Monitoring

In case the study will not be completed at the time of next renewal application, the most current results will be delivered for license renewal, and an interim analysis will be performed with all available data.

4.5 Data Rules

All bleed and infusion data will be entered into the electronic patient diary (hospital infusions will be entered into an eCRF) and imported into SAS. If an infusion is given for a bleed and the bleed information is not provided, the infusion date will be used as the bleed date. Bleeds occurring before start of prophylaxis treatment with study medication will not be counted.

Bleeding rate will be annualized using the following formula:

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 (exclude optional ITI 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.

- "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. Regardless of which bleed is selected, the time of the first bleed in the day will be used. All other infusions in the day for treating bleeds will be considered follow-up infusions.

- "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.

  See example below how these bleeds will be counted.

  - Subject 1 reported => in analysis data set

- Day 5 spontaneous bleed in right knee => bleed as reported
- Day 7 spontaneous bleed in right knee => follow-up infusion
- Day 9 spontaneous bleed in right knee => follow-up infusion
- Day 11 spontaneous bleed in right knee => follow-up infusion

- Subject 2 reported => in analysis data set
  - Day 5 spontaneous bleed in right knee => beed as reported
  - Day 7 follow-up infusion =>as reported
  - Day 9 follow-up infusion => as reported
  - Day 11 spontaneous bleed in right knee => follow-up infusion

Under the 72 hour rule, both subjects will have 1 spontaneous bleed and 3 associated follow/up infusions.

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

When sorting the infusion records for counting number of infusions associated with each bleed, 1st infusions for bleeds will use the bleed date (if missing then use the infusion date). Follow-up infusions will use the dose date.

Joint bleeds can occur in more than 1 joint site. For each joint bleed, count all sites (combining left and right). For the table showing the Joint Site frequency, sum counts over all sites.

4.6 Validity Review

The results of the final data assessment will be documented in the final list of important deviations, validity findings and assignment to analysis set(s). Any changes to the statistical analysis prompted by the results of the review of study data will be documented in an amendment and, if applicable, in a supplement to this SAP.

5. Analysis Sets

5.1 Assignment of analysis sets

Final decisions regarding the assignment of subjects to analysis sets will be made during the review of study data and documented in the final list of important deviations, validity findings and assignment to analysis set(s) (see section 4.6).

Enrolled population

All participants who signed the ICF or had an ICF signed on their behalf by a parent or legal representative

Modified Intent-To-Treat (mITT)

All study participants who have infusion/bleeding data from the EPD and/or CRF will be included in mITT. The mITT population will be used for the efficacy analysis.

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.

Safety analysis set (SAF)

Participants enrolled into the study and received at least 1 dose of study drug will be included in the SAF. The safety population will be used for the safety analysis.

Per protocol set (PPS)

All mITT participants, who completed study treatment and have at least 50 exposure days on study, without important protocol deviations significantly impacting efficacy endpoints will be included in PPS. The detailed definitions and the assignment of subjects to this analysis set will be based on the validity review meeting.

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

Exposure days refers to days with at least one infusion of study drug.

Pharmacokinetic Analysis Set

All participants with evaluable PK data will be included in the pharmacokinetic analysis set.

ITI treatment analysis population

All participants who enter ITI treatment with study intervention will be included in the analysis for ITI treatment.

6. Statistical Methodology

The statistical evaluation will be performed by using the software package SAS release 9.2 or higher (SAS Institute Inc., Cary, North Carolina, United States). All data will be listed and summary tables will be provided. The number of data available and missing data, mean, standard deviation, median, Q1-Q3, minimum and maximum summary statistics will be calculated for continuous data. Frequency tables will be generated for categorical data.

In safety evaluation (vital signs, and laboratory), the last non-missing pre-dose measurement before first study drug administration will be used as baseline.

6.1 Population characteristics

6.1.1 Demography and baseline characteristics

Demographic characteristics, including age, weight, height, BMI will be presented for all subjects and by age groups (<12 or ≥12 years of age) in Part A, and by all subjects in Part B in the form of summary statistics. Other baseline characteristics, including previous treatment characteristics, disease history, target joints, previous number of bleeds, laboratory findings and vital signs, will be handled similarly.

6.1.2 Extent of exposure

Extent of exposure to the study drug, including exposure days, number of days in the study, compliance, frequency of prophylaxis at start and end of study, infusion characteristics [i.e.

number of all infusions, total doses (all infusions), total dose per kg (all infusions), total dose per infusion etc.] will be summarized for each subject receiving any amount of drug. In addition, extent of exposure for surgeries will be summarized separately.

Compliance of each patient will be calculated as below:

Prophylaxis infusion Compliance = 100%* number of actual prophylaxis infusion / number of planned prescribed prophylaxis infusion excluding the bleeding and surgery period

The bleeding and surgery period is defined as the first infusion for a bleed/surgery until next administered prophylaxis infusion.

6.2 Efficacy

All efficacy analyses will be performed on the mITT population. In case more than 5% of participants in one arm (children or adolescents/adults) are excluded from the mITT population, the analyses for primary and secondary endpoints will be repeated in the PP population.

6.2.1 Primary Endpoint(s)

The primary endpoint in Part A is the ABR of all bleeding episodes (sum of spontaneous bleeds and trauma bleeds exclude bleeding due to surgery) 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 (sum of spontaneous bleeds and trauma bleeds exclude bleeding due to surgery) within 48 hours of a previous prophylaxis infusion.

6.2.2 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 (total, joint, spontaneous, trauma)
- 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 total 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

For subjects undergoing surgery (both major and minor), number of surgery infusions, and total doses will be summarized and listed for these subjects.

Factor VIII concentration values and recovery values will be summarized by time point.

recovery = (post-infusion FVIII – pre-infusion FVIII) * weight / dose (in IU)

If a Factor VIII concentration value is below the LLOQ (lower limit of quantification), a data point will be substituted by one half of this limit.

A validity flag for recovery values and their corresponding pre- and post-infusion FVIII values will be created. These values will be considered valid except when any of the following conditions apply:

- If pre-infusion FVIII >= post-infusion FVIII [biologically impossible in the absence of inhibitors]
- If pre-infusion FVIII > 40 IU/dl (note 1 IU/dl=1%) [protocol violation]
- If post-infusion FVIII < 10 IU/dl (note 1 IU/dl=1%) [biologically impossible in the absence of inhibitors]

In the tables displaying descriptive statistics of recovery values, if a recovery is flagged as not valid, then the corresponding pre-infusion FVIII, post-infusion FVIII, and recovery values will not be included.

Furthermore, if there are multiple FVIII values for a subject and timepoint, only the record with the lowest LLOQ will be used. The others values will be excluded from the analysis dataset.

Besides the efficacy variables will be analyzed in summary statistics by age group (<12 or >=12 years of age), if it is applicable, the efficacy endpoints of ABR will also be estimated by a negative binomial regression with duration of treatment period as offset variable.

6.3 Pharmacokinetics/pharmacodynamics

Pharmacokinetic analysis will be only applied for Part A.

The concentration-times courses of FVIII will be tabulated by age groups (<12 or ≥12 years of age; pediatric subgroup of <6y and 6 to <12y; and subgroup of 12-<18y and ≥18y if applicable) for the planned sampling points. The following statistics will be calculated for each of the sampling points (if appropriate): geometric mean, geometric standard deviation (re-transformed standard deviation of the logarithms) and coefficient of variation, arithmetic mean, standard deviation and coefficient of variation, minimum, median, maximum value, and the number of measurements. Geometric means at any time will only be calculated if at least 2/3 of the individual data were measured and were above the lower limit of quantification (LLOQ). For the calculation of the mean value a data point below LLOQ will be substituted by one half of this limit. In tables showing mean values, where values below LLOQ are included in the calculation of mean values, these means will be marked.

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Individual and mean (if appropriate) concentration vs time profiles (using the actual sampling times for individual plots and the planned sampling times for mean plots) will be plotted by

age group (<12 or ≥12 years of age; pediatric subgroup of <6y and 6 to <12y; and subgroup of 12-<18y and ≥18y if applicable) using both linear and semilogarithmic scale.

Pharmacokinetic parameters will be summarized by the statistics mentioned above for each age group (<12 or ≥12 years of age; pediatric subgroup of <6y and 6 to <12y; and subgroup of 12-<18y and ≥18y if applicable).

Individual pharmacokinetic parameters, as well as FVIII levels, will be displayed in subject listings.

6.4 Safety

All safety analyses will be performed on the safety analysis set for overall and by age groups respectively.

6.4.1 Laboratory

Laboratory values, incidence of high or low abnormal values, and shift from baseline with reference laboratory normal ranges, and summary statistics for laboratory values at each visit and changes from baseline (Baseline value is the last value before the first study drug infusion.) will be summarized.

6.4.2 Adverse events

Individual listings of AEs (including age, AEs as reported, start, duration, severity, relation to study drug) will be provided.

For each AE, the number and percentage of subjects who experienced at least 1 occurrence of the AE will be tabulated according to the primary system organ class (SOC) and preferred term (PT) by age groups and overall study population combined.

Frequency tables, showing the number of subjects with drug-related AEs, SAEs, AE related to deaths, AE resulting in permanent discontinuation of study drug, and AESIs will be given.

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. The incidence of treatment-emergent AEs will be summarized using the Medical Dictionary for Regulatory Affairs (MedDRA).

Determination of whether or not an event is treatment-emergent will be derived after the missing or incomplete AE start date is imputed. In case an adverse event starts on the day of first administration of study drug and the time of onset is not known, the event is considered to be not treatment emergent, if it is reported to occur before the first dose of study drug. Details about imputation rules for missing and incomplete AE start are described in section 4.3.

In all other cases the event is considered to be treatment emergent. Inhibitors will be defined as treatment-emergent if they develop after first study drug application.

6.4.3 Adverse Events of Special Interest (AESI)

The adverse events of special interest in this study are:

- *Development of factor VIII inhibitors.*

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 which may be positively associated with development of the inhibitor. Confirmation of the first positive inhibitor titer (≥0.6 BU/mL) which is developed during the treatment with study drug 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.

- *Hypersensitivity and allergic reactions including skin related and systemic reactions, such as anaphylactic reactions, (seriousness should be a case by case decision)*

The incidence of AEs, and AESI will be summarized and described for each age group and also for the overall study population combined.

6.4.4 Vital signs

Vital signs at each visit and change from baseline will be summarized.

7. Document history and changes in the planned statistical analysis

Version	Date	Action
Version 1.0	18 September 2020	
Version 2.0	17 November 2021	• Updated according to Global Integrated Clinical Study Protocol version 2.0. • Updated the Compliance calculation in section 6.1.1 • Detail the ABR of all bleeding episodes in section 6.2.1

8. References

N.A.