# Statistical Analysis Plan

NCT Number: NCT05707351

Title: A Phase 3, Prospective, Multicenter, Open-label Study of Efficacy, Safety, and Pharmacokinetics of PEGylated Recombinant Factor VIII (ADYNOVATE) Administered for Prophylaxis and Treatment of Bleeding in Chinese Previously Treated Patients With Severe Hemophilia A (FVIII <1%)

Study Number: TAK-660-3001

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# STATISTICAL ANALYSIS PLAN

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Study Phase: Phase 3

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Prepared by: [redacted]

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## REVISION HISTORY

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|---|---|---|
| Original version | 08-Dec-2022 | Not Applicable |
| Amendment 1 | 30-Aug-2024 | To update SAP to be consistent with Protocol Amendment 1 |

## TABLE OF CONTENTS

## LIST OF IN-TEXT TABLES

## ABBREVIATIONS

| | |
|---|---|
| ABR | annualized bleeding rate |
| AE | adverse event |
| AJBR | annualized joint bleeding rate |
| ALT | alanine aminotransferase |
| aPTT | activated partial thromboplastin time |
| AST | aspartate aminotransferase |
| AUC | area under the concentration versus time curve between defined timepoints |
| BE | Bleeding episode |
| BU | Bethesda unit(s) |
| CHO | Chinese hamster ovary |
| CI | confidence interval |
| CL | clearance |
| $C_{max}$ | maximum concentration |
| COVID-19 | coronavirus disease of 2019 |
| CPAP | Clinical Pharmacology Analysis Plan |
| $C_{predose}$ | predose concentration |
| CRA | clinical research associate |
| CRO | contract research organization |
| EC | ethics committee |
| eCRF | electronic case report form |
| ED | exposure day |
| eDiary | electronic diary |
| EHL | extended half-life |
| ELISA | enzyme-linked immunosorbent assay |
| EMA | European Medicines Agency |
| ePRO | electronic patient-reported outcome |
| EQ-5D-5L | European Quality of Life Questionnaire in 5 dimensions 5-level version |
| EUDRACT | European Union clinical trials database |
| FAS | full analysis set |
| FDA | Food and Drug Administration |
| FIX | factor IX |
| FVIII | factor VIII |
| GCP | Good Clinical Practice |
| GHEA | Global Hemostatic Efficacy Assessment |
| HCV | hepatitis C virus |
| HIV | human immunodeficiency virus |
| HRQoL | health-related quality of life |
| HRU | Healthcare resource utilization |
| IB | investigator's brochure |
| ICF | informed consent form |
| ICH | International Council for Harmonisation |
| IND | investigational new drug |
| INR | international normalized ratio |
| IP | investigational product |
| IR | incremental recovery |
| IRB | institutional review board |
| IU | international units |
| MRT | mean residence time |
| NCA | noncompartmental analysis |

| | |
|---|---|
| PEG | polyethylene glycol |
| PK | pharmacokinetic(s) |
| PK AS | pharmacokinetic analysis set |
| PK FAS | pharmacokinetic full analysis set |
| PPAS | per protocol analysis set |
| pRBC | packed red blood cell |
| PRO | patient-reported outcome |
| PT | preferred term |
| PTP | previously treated patient |
| PUP | previously untreated patient |
| rFVIII | recombinant human coagulation factor VIII |
| RSI | reference safety information |
| SAE | serious adverse event |
| SAP | statistical analysis plan |
| SA set | safety analysis set |
| SD | standard deviation |
| SOC | system organ class |
| STEAE | serious treatment-emergent adverse event |
| SUSAR | suspected unexpected serious adverse reaction |
| SWFI | sterile water for injection |
| $T_{1/2}$ | half-life |
| UADE | unanticipated adverse device effect |
| TEAE | treatment-emergent adverse event |
| ULN | upper limit of normal |
| US | United States |
| V | volume of distribution |
| VWF | von Willebrand factor |

# 1.0 OBJECTIVES, ENDPOINTS, AND ESTIMANDS

## 1.1 Study Objectives

### 1.1.1 Primary Objective

*The primary objective of this study is to assess the efficacy of ADYNOVATE for prophylactic treatment in previously treated Chinese subjects with severe hemophilia A based on the total annualized bleeding rate (ABR).*

### 1.1.2 Secondary Objective(s)

*The secondary objectives of this study are:*

- *To assess the efficacy of ADYNOVATE for prophylactic treatment based on ABR by bleeding site and cause*
- *To assess the overall hemostatic efficacy rating of ADYNOVATE for treatment of nonsurgical breakthrough bleeding episodes during the study period*
- *To assess the efficacy of ADYNOVATE for perioperative bleeding management if minor surgery is performed during the study period*
- *To evaluate the safety of ADYNOVATE as assessed by adverse events (AEs) and serious AEs (SAEs) as well as clinically significant findings in vital signs and clinical laboratory parameters*
- *To evaluate the safety and the immunogenicity of ADYNOVATE based on the incidence of factor VIII (FVIII) inhibitory antibodies and binding antibodies to ADYNOVATE*
- *To evaluate the pharmacokinetics (PK) of ADYNOVATE in Chinese subjects*



### 1.1.3 Exploratory Objective(s)

- *To assess the effect of ADYNOVATE on health-related quality of life and healthcare resource utilization*

## 1.2 Study Endpoints

**Table 1. Objectives and Endpoints**

| Objective | Endpoint(s) |
|---|---|
| **Primary** | |
| • *To assess the efficacy of ADYNOVATE for prophylactic treatment in previously treated Chinese subjects with severe hemophilia A based on the total ABR* | • *Total ABR* |
| **Secondary** | |
| • *To assess the efficacy of ADYNOVATE for prophylactic treatment based on ABR by bleeding site and cause* | • *Annualized bleeding rates based on bleeding site and cause*<br>• *Number of infusions and weight-adjusted consumption of ADYNOVATE per week and month during the prophylactic treatment period*<br>• *Proportion of subjects with zero bleeding episodes during the study*<br>• *Time intervals between bleeding episodes* |
| • *To assess the overall hemostatic efficacy rating of ADYNOVATE for treatment of nonsurgical breakthrough bleeding episodes during the study period* | • *Overall hemostatic efficacy rating at bleed resolution for treatment of breakthrough bleeding episodes*<br>• *Number of infusions and weight-adjusted consumption of ADYNOVATE per bleeding episode* |
| • *To assess the efficacy of ADYNOVATE for perioperative bleeding management if minor surgery is performed during the study period* | • *Overall assessment of hemostatic efficacy based on the GHEA score as assessed by the operating surgeon/investigator*<br>• *Intra- and postoperative actual versus predicted blood loss after the surgery, at postoperative day 1, and at discharge as assessed by the operating surgeon/investigator*<br>• *Perioperative transfusion requirement of blood, red blood cells, platelets, and other blood products*<br>• *Daily intra- and postoperative weight-adjusted consumption dose of ADYNOVATE* |
| • *To evaluate the safety of ADYNOVATE as assessed by AEs and SAEs as well as clinically significant findings in vital signs and clinical laboratory parameters* | • *Occurrence of AEs and SAEs, total incidence, by severity, and by causality*<br>• *Occurrence of thromboembolic events and hypersensitivity reactions*<br>• *Clinically significant changes in vital signs and clinical laboratory parameters* |

## Table 1. Objectives and Endpoints

| Objective | Endpoint(s) |
|---|---|
| • *To evaluate the safety and the immunogenicity of ADYNOVATE based on the incidence of FVIII inhibitory antibodies and binding antibodies to ADYNOVATE* | • *Immunogenicity: Development of confirmed inhibitory antibodies (≥0.6 BU/mL using the Nijmegen modification of the Bethesda assay) to FVIII*<br>• *Binding antibodies to ADYNOVATE*<br>• *Binding antibodies to CHO proteins* |
| • *To evaluate the PK of ADYNOVATE in Chinese subjects* | • *Factor VIII activity (1-stage clotting assay) in PK samples collected for single-dose and steady-state PK assessments*<br>• *Incremental recovery over time during prophylactic treatment at ED1, Week 6 (approximately ED10 to ED15), and ED50*<br>• *Predose FVIII (activity and antigen) and VWF (antigen) at scheduled visits*<br>• *Pharmacokinetic parameters including CL, V, AUC, $C_{max}$, $C_{predose}$, and elimination phase $T_{1/2}$, following a single dose and steady-state dosing, using NCA methodology, subject to data availability* |
| **Exploratory** | |
| • *To assess the effect of ADYNOVATE on health-related quality of life and healthcare resource utilization* | • *Health-related quality of life as assessed using the European Quality of Life Questionnaire in 5 Dimensions 5-level version (EQ-5D-5L)*<br>• *Healthcare resource utilization endpoints, including number and duration of hospitalizations, number of emergency room visits, number of acute care visits, and number of days missed from school/work* |



*ABR=annualized bleeding rate; AE=adverse event; AUC=area under the concentration versus time curve between defined timepoints; BU=Bethesda unit(s); CHO=Chinese hamster ovary; CL=clearance; $C_{max}$=maximum concentration; $C_{predose}$=predose concentration; ED=exposure day; FVIII=factor VIII; GHEA=Global Hemostatic Efficacy Assessment; NCA=noncompartmental analysis; PK=pharmacokinetic(s); PRO=patient-reported outcome; SAE=serious adverse event; $T_{1/2}$=half-life; V=volume of distribution; VWF=von Willebrand factor*

### 1.3 Estimand(s)

**Table 1.a Estimand Framework**

Estimand: Primary

| | Attributes | | | | |
|---|---|---|---|---|---|
| **Definition** | **Treatment** | **Population** | **Variable (or Endpoint)** | **Strategy for Addressing Intercurrent Event** | **Population-Level Summary** |
| The primary estimand is the total annualized bleeding rate (ABR) in a Full Analysis Set (FAS) of subjects with severe Hemophilia A who are previously treated, Chinese, 12 to 65 years of age at screening and male, and have prophylactic treatment with ADYNOVATE (rurioctocog alfa pegol). | ADYNOVATE, following reconstitution, is injected intravenously using an appropriately sized syringe as a bolus infusion in ≤ 5 minutes (maximum infusion rate, 10 mL/min). | Study subjects identified per inclusion and exclusion criteria as stated in the protocol who are assigned to receive a treatment regimen of ADYNOVATE (FAS) | Total ABR is calculated as the number of bleeding episodes (BEs) divided by the number of days on prophylactic treatment with ADYNOVATE (rurioctocog alfa pegol) in years (i.e. [number of BEs/(number of days on the treatment / 365.25)]). | The duration of the on-treatment observation period may vary due to early discontinuation from the study. The variation will be addressed by annualization of the bleeding rate. | Treatment means (point estimates with corresponding 95% CIs) of total annualized bleeding rate (ABR) will be estimated with negative binomial regression using bleeding episodes during the on-treatment observation period of prophylactic treatment phase.<br>ABR will also be summarized with descriptive statistics. |



## 2.0 STUDY DESIGN

### 2.1 Overall Design

*This Phase 3, prospective, multicenter, open-label study will evaluate the efficacy and safety of ADYNOVATE for prophylaxis and treatment of bleeding episodes in previously treated patients (PTPs) with severe hemophilia A (FVIII <1%) in the Chinese population. The study will also provide ADYNOVATE PK data in Chinese patients with severe hemophilia A. The overall study flow chart is illustrated in Figure 1 (Section 9.4).*

*It is planned to enroll at least 30 evaluable Chinese subjects aged 12 to 65 years. All subjects and/or legal representatives are required to provide signed informed consent. For screening, subjects need to undergo a minimum washout period of at least 72 to 96 hours following their*

*last FVIII therapy (on-demand or prophylactic), if applicable. Thereafter, the study screening procedures (Table 2 in Section 9.5) will be performed for eligibility determination and will be completed within 30 days prior to the initial PK assessment (if applicable) or baseline visit. Screening procedures will include demographics, medical/medication history, concomitant medications, AEs, physical examination, vital signs, and clinical laboratory assessments (Table 3 in Section 9.5). Medical history (including immunization history) will include surgery history, hemophilia history, bleeding episode history, and history of FVIII usage over the last year. Target joints and subject's ABR based on the previous 9 to 12 months will also be recorded. Medication history will include the name of the product, dose, dosing interval, and regimen start and end date.*

*All enrolled subjects will receive twice-weekly prophylactic treatment with ADYNOVATE (45±5 IU/kg) over a period of 26 weeks (+2 weeks) or at least 50 EDs, whichever occurs last.*

*Pharmacokinetic evaluation is planned to be performed in at least 12 evaluable subjects. For subjects participating in the PK portion of the study, the initial PK assessment will be performed after a washout period of at least 72 to 96 hours following their last FVIII therapy (if applicable) and prior to the baseline visit. The second PK assessment will be performed during the Week 20 (±1 week) visit following the scheduled prophylactic treatment dose. The PK samples will be collected at specified time points and measured for FVIII activity by a 1-stage clotting assay. For subjects not participating in the PK portion, the baseline visit will be initiated immediately upon eligibility confirmation.*

*Following the baseline visit, subjects will return to the study site for study treatment visits at the below timepoints for the efficacy and safety assessments:*

- *Week 2 (±1 week)*
- *Week 6 (±1 week)*
- *Week 12 (±1 week)*
- *Week 20 (±1 week) (only for subjects undergoing PK assessment)*
- *Study Completion/Termination Visit: Week 26 (+2 weeks) or at least 50 EDs (whichever occurs last)*

*All other study treatments may be administered either at a clinic/hospital/study site or at home by self-administration/administration by a parent/caregiver. The investigator will determine the setting of treatment administration. Unscheduled visits may occur between scheduled site visits as required. Assessments may be performed as clinically indicated at the discretion of the investigator.*

*Factor VIII (activity and antigen) and VWF antigen levels will be measured at specified study visits, preinfusion, in both PK and non-PK subjects. During the baseline visit, Week 6 visit, and the study completion/termination visit, peak levels of FVIII activity will also be assessed within 30 minutes before ADYNOVATE administration and 30±10 minutes post ADYNOVATE infusion for the determination of incremental recovery (IR). The IR determination at the baseline visit will*

*only be performed in subjects who have not undergone initial PK assessment. All PK samples collected in this part will be used, along with the samples collected in the PK assessments, to characterize PK properties in PTPs across age groups.*

*At each study visit, investigators will review subject electronic diaries (eDiaries) for prophylactic treatment compliance, bleeding episodes and treatment, AEs, concomitant medications, and nondrug therapies. The PRO assessment, using the European Quality of Life Questionnaire in 5 Dimensions 5-level version (EQ-5D-5L), will be captured via an electronic PRO (ePRO) device. Subjects should complete the EQ-5D-5L prior to baseline visit (or initial PK assessment for subjects participating in the PK portion of the study) and study completion/termination visit. Healthcare resource utilization will be gathered by sites via questionnaire as part of the electronic case report form (eCRF). Upon completion of prophylactic treatment (at least 50 EDs or 26 weeks [+2 weeks], whichever occurs last), the study site will follow up via phone call with each subject after 3 to 5 days to determine the occurrence of AEs.*

*During the study period, subjects will also be treated for breakthrough bleeding episodes with ADYNOVATE. The dose and frequency of ADYNOVATE administration will be individualized based on the subject's weight, type and severity of bleeding episode, and monitoring of appropriate clinical and laboratory measures per the investigator's judgment (as described in Protocol Section 6.2.2.3).*

*If a subject requires minor elective or emergency surgical, dental, or other invasive procedures during the study after enrollment (ie, a surgery that was not planned before study enrollment), perioperative bleeding will be managed with ADYNOVATE. The dose and frequency of ADYNOVATE administration will be individualized based on the subject's IR to obtain the FVIII target level required for the procedure being performed (as described in Protocol Section 6.2.2.4). Major surgeries are not in the scope of this study; any required major surgery will result in the withdrawal of the subject.*

*The primary objective of this study is to assess the efficacy of ADYNOVATE for prophylactic treatment in previously treated Chinese subjects with severe hemophilia A based on the total ABR.*



## 2.2 Scientific Rationale for Study Design

*The design of this study is based on a previously completed multinational confirmatory study (Study 261201). The study design, including endpoints, study population, and inclusion/exclusion criteria, are all supported by the results of previous global studies in this program (refer to Protocol Section 2.2).*

## 2.3 Justification for Dose

*Pharmacokinetic results from global studies with ADYNOVATE showed similar results between the Chinese/Asian subjects and the overall study populations, suggesting ethnic insensitivity of ADYNOVATE PK. Further, efficacy was demonstrated across age groups and ethnicities,*

*indicating that ADYNOVATE is a non–ethnically sensitive EHL rFVIII from which Chinese adult and adolescent subjects may benefit. Thus, the doses and regimen of the current study are considered to be appropriate.*

### 2.4 Duration of Subject Participation and Study Completion Definition

*All enrolled subjects will receive twice-weekly prophylactic treatment with ADYNOVATE over a period of 26 weeks (+2 weeks) or at least 50 EDs, whichever occurs last. Each subject's maximum duration of participation is expected to be approximately 8 months unless prematurely discontinued.*

*Study completion is defined as the date on which the last subject in the study completes the final protocol-defined assessments and includes the safety follow-up conducted via phone 3 to 5 days following prophylactic treatment completion (refer to Protocol Section 8.1.4 for the defined follow-up period for this protocol). The total study duration will be approximately 3 years.*

### 2.5 Sites and Regions

*The study will be conducted at approximately 12 sites in China.*

### 2.6 Study Stopping Rules

*The study will be halted (enrollment and treatment temporarily suspended), or stopped (enrollment and treatment permanently discontinued), pending further review by sponsor, if one or more of the following criteria are met:*

1. *If 2 or more subjects develop a high responder inhibitory antibody (>5 BU), confirmed by 2 separate measurements within 2 weeks at the central laboratory, after ADYNOVATE administration*
2. *If 2 or more subjects develop anaphylaxis caused by the exposure to ADYNOVATE*

*The study may be terminated if one or more of the following criteria are met:*

1. *The sponsor decides to terminate the study based upon its assessment of safety*
2. *The sponsor decides to terminate the study for administrative reasons*

## 3.0 STATISTICAL HYPOTHESES AND DECISION RULES

### 3.1 Statistical Hypotheses

This is a single arm, open-label study. There is no formal statistical hypothesis for the study.

### 3.2 Statistical Decision Rules

Not applicable.

### 3.3 Multiplicity Adjustment

Not applicable.

## 4.0 SAMPLE SIZE DETERMINATION

*At least 30 evaluable adult and adolescent subjects (aged 12 to 65 years) will be enrolled. The sample size was not based on statistical consideration. The evaluable subjects are defined as all subjects who are treated with ADYNOVATE for a minimum of 50 EDs or approximately 26 weeks (+2 weeks), whichever occurs last. Subjects who withdraw or discontinue before study completion may be replaced.*

## 5.0 ANALYSIS SETS

### 5.1 Screened Set

The screened set will comprise all subjects who sign the informed consent form (ICF).



### 5.2 Safety Analysis Set

*The safety analysis set (SA set) will comprise all subjects treated with at least 1 ADYNOVATE dose. All safety analyses will be performed on the SA set.*

### 5.3 Full Analysis Set

*The full analysis set (FAS) will comprise all subjects who are assigned to receive a treatment regimen of ADYNOVATE. All efficacy analyses will be performed on the FAS.*

### 5.4 Per-Protocol Analysis Set

*The per protocol analysis set (PPAS) will comprise all subjects who were treated with the prophylaxis Adynovate treatment regimen and comply with their originally assigned dose for the duration of study participation. The subjects who are not complied with the assigned doses will be captured in the protocol deviation log which will be reviewed and finalized before the database lock. The PPAS will be the supportive analysis set.*

### 5.5 Pharmacokinetic Full Analysis Set

*The PK full analysis set (PK FAS) will comprise all subjects who consented to PK evaluation, were treated with at least 1 ADYNOVATE dose, and have at least 1 evaluable PK concentration post dose. All PK analyses will be performed on the PK FAS.*

### 5.6 Pharmacokinetic Analysis Set

*The PK analysis set (PK AS), a subset of the PK FAS, will comprise all PK subjects who received at least 1 ADYNOVATE PK dose with a sufficient number of evaluable PK concentrations post dose for the estimation of PK parameters using a noncompartmental analysis (NCA).*

# 6.0 STATISTICAL ANALYSIS

## 6.1 General Considerations

Please refer to Section 9.2.2 for handling of missing data.

### 6.1.1 Handling of Treatment Misallocations

Not applicable.

### 6.1.2 Analysis Approach for Continuous Variables

In general, all continuous variables will be summarized and tabulated with descriptive statistics including the number of subjects with non-missing values, mean (SD), median, the 1st and 3rd quartiles, minimum and maximum values, unless otherwise specified. The above descriptive statistics will only be presented if there are at least 3 results available in a group. All statistics except median and the 1st and 3rd quartiles will be presented if only 2 results are available in a group while only the number of subjects and mean will be presented if only 1 result is available in a group.



### 6.1.3 Analysis Approach for Binary/Categorical Variables

In general, categorical/binary variables will be summarized using the counts and proportions of each possible value. The denominator for the proportion will be based on the number of subjects in corresponding analysis set, unless otherwise specified.

### 6.1.4 Analysis Approach for Time-to-Event Variables

Not applicable.

## 6.2 Disposition of Subjects

All subjects, or their legal representatives, as required, that provide informed consent (i.e., signs and dates the informed consent form and assent form, if applicable) will be accounted for in this study. An individual subject's participation starts once informed consent has been provided and ends at the completion/termination visit.

Subject treatment period is approximately 6 months (26 weeks [+2 weeks], or at least 50 EDs, whichever occurs last) from enrollment to the subject completion of the study, unless prematurely discontinued.

A list of Screen Failures will be presented in a listing including reasons recorded in eCRF.

A summary of disposition and analysis sets will be presented in a table for Screened Set.

The number and percentage of subjects who prematurely discontinued from the study treatment will be presented overall. Reasons for premature discontinuation from the study treatment will be summarized (number and percentage) overall. The number and percentage of subjects who completed and prematurely discontinued from the study will be presented overall. Reasons for

premature discontinuation from the study, as recorded on the *end of study* page of the eCRF, will be summarized (number and percentage) overall. Subjects who prematurely discontinued from the study will be listed by discontinuation reason.

## 6.3 Protocol Deviations

Protocol deviations will be collected and will be classified as significant, or non-significant. The CRO and sponsor will review the protocol deviations and their classification for accuracy throughout the study and before final database lock.

Protocol deviation will be summarized by pre-defined categories (eg. informed consent form, missing dose) as well as by class (significant, or non-significant).

## 6.4 Demographic and Other Baseline Characteristics

### 6.4.1 Demographic Characteristics

Demographic characteristics will be summarized descriptively for overall for the FAS and SA Set (if different from FAS).

The following demographic characteristics will be summarized in a table:

- Age (years) at inform consent
- Age group (12 years - <18 years, >=18 years - 65)
- Weight (kg)
- Height (cm)
- BMI, calculated as weight (kg) / [height (cm) / 100]$^2$

All demographics will be listed.



### 6.4.2 Medical History

Medical history will be collected at screening and recorded on the eCRF and will be coded using the version of the Medical Dictionary for Regulatory Activities (MedDRA) which is specified in the data management coding guidelines, including:

- Immunization history
- Surgery history
- Bleeding episode history

These data will be summarized for subjects in the SA Set for overall. Listings will be provided using the SA Set as well.

### 6.4.3 Baseline Characteristics

Baseline characteristics will be summarized by age group (12 years - < 18 years and >= 18 years – 65 years) and for overall, as outlined below.

- ABO Blood type

- Target joint category (number of target joints: 0, 1, 2, 3, ⩾4)
- Subject's ABR based on the previous 9 to 12 months
- Hepatitis C Virus Antibody
- HIV Antibody

## 6.5 Medication History and Concomitant Medications

Prior and concomitant medications will be analyzed based on the SA Set.

### 6.5.1 Prior Medications

All non-study treatments (including but not limited to herbal treatments, vitamins, behavioral treatment, nonpharmacological treatment, such as psychotherapy) received within 30 days prior to the informed consent will be considered as prior medications for the study.

Prior medications and non-drug therapies will be coded to a preferred term (PT) using the World Health Organization (WHO) Drug Dictionary Global. The prior medication usage will be summarized by the number and percentage of subjects who used each medication or therapy, and by PT. Multiple medication/therapy usage by a subject in the same category will be counted only once.



Missing or partial dates will be imputed as described in Section 9.2.2 prior to determining whether a medication or non-drug therapy is prior or concomitant.

In addition to prior medications described above, the following data about medication history will be summarized for the subjects in the SA set for overall. Listings will be provided as well:

- Previous use of FVIII products used within the previous 12 months (name of the medication, dose, dosing interval, and regimen start and end date)
- Any PEGylated medication (name of drug, indication, and dates of use)
- Fresh frozen plasma, cryoprecipitate, and/or any type of FVIII concentrate
- Any kind of blood transfusion, such as pRBCs, platelets, or plasma

### 6.5.2 Concomitant Medications

Concomitant treatment refers to all treatments other than the investigational product (IP) taken from the time informed consent is signed until end of the safety follow-up period. Concomitant treatment information will be recorded on the eCRF and in the subject's eDiary.

Concomitant medications will be coded using the same dictionary as prior medications. Concomitant medications will be summarized by the number and percentage of subjects receiving each medication by dictionary term. Multiple medication usage by a subject in the same category will be counted only once.

Missing or partial dates will be imputed as described in Section 9.2.2 prior to determining whether a medication or non-drug therapy is prior or concomitant. All prior and concomitant medications and non-drug therapies will be listed for the SA Set.

## 6.6 Efficacy Analysis

All efficacy analyses will be performed on the Full Analysis Set.

### 6.6.1 Primary Endpoint(s) Analysis

Primary efficacy endpoint is the total annualized bleeding rate (ABR) during the study treatment (from the first dose of IP to the last dose of IP, inclusive).

#### 6.6.1.1 Derivation of Primary Efficacy Endpoint

Total annualized bleeding rate (ABR) is defined as both treated and non-treated bleeding episodes occurred during the treatment period and will be derived on the subject-level as:

$$ABR = \frac{Number\ of\ unique\ bleeds\ occured\ during\ treatment\ period}{Length\ of\ treatment\ period\ (\text{days})/365.25}$$

Treatment period (days) will be calculated as (date of last dose of IP – date of the first dose of IP + 1).

#### 6.6.1.2 Main Analytical Approach for Primary Efficacy Endpoint

Total ABR will be summarized in descriptive statistics. In addition, mean ABR and corresponding 95% confidence interval will be estimated with a generalized linear model framework with the negative binomial distribution. Model options will include the logarithm of the duration of the treatment period (in years) as an offset.

The following SAS® code will be used:

```
proc genmod data= <dataset>;
model <number of bleeds during the treatment period >=  /dist=negbin
offset=ln<duration of the treatment period in years>;
run;
```



#### 6.6.1.3 Sensitivity Analysis

The analyses which are described as primary analyses (Section 6.6.1.2) will be conducted in the PPAS as sensitivity analyses.

### 6.6.2 Secondary Endpoint(s) Analysis

All analysis of secondary efficacy endpoints will be based on the FAS.

#### 6.6.2.1 Bleeding Episodes and Annualized Bleeding Rate Based on Bleed Type

Number of bleeding episodes (treated and untreated) and ABR will also be summarized descriptively by type of bleeding (ie, spontaneous (ie, not related to injury/trauma), injury (definitely due to injury/trauma)).

#### 6.6.2.2 Consumption of ADYNOVATE

Number of infusions and the amount of ADYNOVATE consumptions (IU or IU/kg) per week, per month, and overall for prophylactic treatment during the treatment period will be summarized descriptively based on the FAS.

Treatment of bleeding episodes (excluding surgeries) including total number of infusions and the amount for all treated bleeding episodes and number of infusions and the amount ADYNOVATE consumptions (IU or IU/kg) for each treated bleeding episode during the treatment period will be summarized descriptively based on the FAS.

The total number of EDs will be summarized descriptively based on the FAS.

Please refer to Section 6.7.6 for details regarding the calculations.

#### 6.6.2.3 Zero Bleeding Episodes

Total ABR during the study will be categorized as 0, >0. Proportion of subjects with zero bleeding episodes (as in ABR category of 0) during the study will be presented.

#### 6.6.2.4 Time Interval Between Bleeding Episodes

Time interval between 2 consecutive unique bleeding episodes will be summarized descriptively using averaged time interval computed for each subject as the duration of the treatment period divided by the number of unique bleeding episodes in the treatment period.

#### 6.6.2.5 Hemostatic Efficacy Rating

The overall hemostatic efficacy rating (Excellent, Good, Fair, None) at resolution of each bleeding episode will be summarized by frequency table and by severity (mild, moderate, or severe) of bleeding for all treated bleeding episodes.

#### 6.6.2.1 Efficacy for Surgery

The overall assessment of hemostatic efficacy based on the Global Hemostatic Efficacy Assessment (GHEA) score, as assessed by the operating surgeon/investigator, will be summarized by frequency table for all minor surgeries.

Intra- and postoperative actual versus predicted blood loss after the surgery, at postoperative day 1, and at discharge as assessed by the operating surgeon/investigator will be summarized using descriptive statistics for minor surgeries.

Number and percent of subjects who have any surgeries and require perioperative transfusion of blood, red blood cells, platelets, and other blood products will be summarized by frequency table for minor surgeries. The volume of transfusions will be summarized using descriptive statistics for each surgery.

Daily intra- and postoperative weight-adjusted consumption dose of ADYNOVATE will be summarized using descriptive statistics for minor surgeries.

### 6.6.3 Subgroup Analyses

Primary efficacy endpoint with descriptive statistics and the following secondary efficacy endpoints will be summarized by age group (12 years - < 18 years and >= 18 years – 65 years) as specified in Section 6.4.1.

- Annualized bleeding rates based on bleeding site and cause
- Number of infusions and weight-adjusted consumption of ADYNOVATE per week and month during the prophylactic treatment period
- Proportion of subjects with zero bleeding episodes during the study
- Time intervals between bleeding episodes
- Overall hemostatic efficacy rating at bleed resolution for treatment of breakthrough bleeding episodes
- Number of infusions and weight-adjusted consumption of ADYNOVATE per bleeding episode

The following endpoints will be summarized in the subgroup of evaluable subjects as defined in Section 4.0.

- Annualized bleeding rates
- Annualized bleeding rates based on bleeding site and cause
- Proportion of subjects with zero bleeding episodes during the study



## 6.7 Safety Analysis

The safety analysis will be performed using the SA Set. Safety variables collected in eCRF including AEs, immunogenicity, clinical laboratory results, and vital signs will be summarized. For each safety variable, the last observed value collected before the first dose of IP will be used as baseline for all analyses of that safety variable.

### 6.7.1 Adverse Events

For this study, any untoward medical occurrence occurring from the time the ICF is signed will be considered an AE.

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA).

A treatment-emergent adverse event (TEAE) is any AE emerging or manifesting at or after the initiation of treatment with an IP or any existing event that worsens in either intensity or frequency following exposure to the IP. Only TEAEs will be summarized.

The following analyses will be performed with incidence (%) and number of events:

- Overall summary of TEAEs:
  - Any TEAEs
  - Severe TEAEs (as per medical assessment)
  - Serious TEAEs (STEAEs)
  - TEAEs/STEAEs related to IP based on investigator assessment of causality
  - TEAEs leading to study drug withdrawal
  - TEAEs leading to death
- Summaries of TEAEs by PT only, in descending order of overall incidence for:
  - All TEAEs
  - TEAEs occurring in ≥10% of subjects
- Summaries by SOC and PT: The number and percentage of subjects reporting AEs and the number of AEs will be summarized and tabulated for overall. SOC will be presented alphabetically. PT within SOC will be presented by descending incidence. The analysis will be done for the following groups of AEs:
  - Any TEAEs
  - Any study-treatment-related TEAEs
  - Serious TEAEs
  - Study-treatment-related STEAEs
  - TEAEs leading to study drug withdrawal
  - TEAEs leading to death
- Summaries by SOC, PT, and maximum severity: SOC will be presented alphabetically. PT within SOC will be presented by descending incidence in the combined subject groups (where applicable). Within PT, events will be sorted by maximum severity (mild, moderate, severe and total). The number and percentage of subjects reporting AEs and the number of events will be tabulated by SOC, PT and maximum severity.
- In addition, the following TEAEs will also be summarized separately:
  - Hypersensitivity reactions
  - Anaphylactic reaction and severe hypersensitivity reactions as identified by the investigator.
  - Thromboembolic Events



All TEAEs will also be summarized by age groups.

All AEs will be listed. The listing will include Subject identifier, age, system organ class / preferred term / reported term of the AE, duration, severity, seriousness, action taken, outcome, causality assessment by investigator, onset date, stop date, and death. Separate listings of serious AEs, AEs which led to discontinuation, and AEs which led to death will be generated.

### 6.7.2 FVIII Inhibitor/Antibody Development

Immunogenicity assessments including the measurement of inhibitory antibodies to FVIII and binding antibodies to ADYNOVATE will be collected at Screening, Baseline, Weeks 2, 6, 12, and Study Completion/Termination Visit (Week 26). A minimum washout of 72 to 96 hours is required following the last infusion of any other nonmodified FVIII therapy and 84 to 96 hours

following the last infusion of ADYNOVATE. Binding antibodies to CHO protein will be included in immunogenicity assessment only at the screening visit, Week 12, and the Study Completion/Termination Visit.

Inhibitor and binding antibody results (including the titer, should the result be positive) specific to the forming of antibodies include:

- Inhibitory antibodies to FVIII
- Binding antibodies to Adynovate
- Binding Antibodies to CHO proteins

Results of inhibitory antibodies to FVIII, according to the Nijmegen modification of the Bethesda assay are defined as follows:

- Positive for inhibitor development with titer of ≥ 0.6 BU/mL
- Negative for inhibitor development with titer of < 0.6 BU/mL

Results of binding antibodies to ADYNOVATE are defined as follows:

- Positive: Any result confirmed positive
- Negative: Any result that screened negative or confirmed negative
- Ab titer: any confirmed positive samples will be assessed for antibody tier, and reported

Results of binding antibodies to CHO proteins results are defined as follows:

- Positive: Any result confirmed positive
- Negative: Any result that screened negative or confirmed negative
- Ab titer: any confirmed positive samples will be assessed for antibody tier, and reported

The proportion of subjects that developed inhibitory antibodies to FVIII (confirmed by the 2nd repeated blood sample within weeks of the 1st positive blood sample) at any time during the study will be summarized, together with exact Clopper-Pearson 95% confidence intervals for the proportion.

The SAS® code to be used in the Clopper-Pearson analysis is:

```
PROC FREQ DATA = <ds>;
  WEIGHT <count>;
  TABLES <result> / BINOMIAL (EXACT CP) ALPHA = 0.05 CL;
RUN;
QUIT;
```

where <ds> refers to the input dataset, <count> the number of subjects with a particular result and <result> to the actual result, i.e., "Yes" or "No".

Histograms will be used to show the number and proportion of subjects with binding antibodies to ADYNOVATE and binding antibodies to CHO proteins.

Inhibitory antibodies to FVIII and binding antibodies to ADYNOVATE will be summarized for the SA Set.

In addition, the risk factors of the development of inhibitor will be explored with exposure of dosage (IU, IU/kg) prior to the inhibitor onset, number of EDs prior to the inhibitor onset, and surgeries (yes/no) prior to the inhibitor onset.

The Ab status will be classified as pre-existing Ab (Ab positive before first dosing), treatment-induced Ab response (baseline negative), treatment-boosted Ab response (Ab titer increased >4 folds for subject with preexisting Ab), transient positive and persistent positive for each subject.

### 6.7.3 Clinical Laboratory Evaluations

The clinical laboratory tests (the complete list of clinical lab tests specified in Protocol Appendix 2) will be collected for each study visit. The analyses of immunogenicity are described in previous section (Section 6.7.2).

Laboratory parameters will be presented using controlled terminology and standard international (SI) units.

Descriptive statistics for laboratory results by visit will be summarized for the SA Set.

Shift tables will summarize number (%) of subjects who had lab results in low, normal, high at baseline and at the last lab test during study to evaluate the change of lab values for clinically relevant lab parameters including hematology, clinical chemistry, and lipids.

Number (%) of subjects with clinically significant lab results evaluated by investigators for each lab parameter will be summarized.

Laboratory results for all parameters (planned or unplanned) will be listed for the SA Set, including separate listings for abnormal and clinically significant results.



### 6.7.4 Vital Signs

Vital signs will be collected at each study visit. The time points for pre- and postinfusion measurements are within 30 minutes before infusion start (prior to blood sample collection) and 30±15 minutes after infusion. Weight is measured preinfusion only.

Vital signs including Pulse Rate (bpm), Respiratory Rate (breaths/min), Temperature (ºC), Systolic Blood Pressure (mmHg), and Diastolic Blood Pressure (mmHg) will be summarized at baseline and each post-baseline visit and at each time point (if applicable) descriptively. The changes from baseline of vital signs will be summarized at each post-baseline visit and at each time point (if applicable) descriptively.

Number (%) subjects with abnormal vital signs (out of vital sign normal ranges) will be summarized. The vital sign normal ranges are specified in FDA Guidance for Industry of Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials (September 2007). Shift tables of changes in toxicity grading will be used to assess the changes from baseline to the worst post-baseline cases (in both directions of change, if applicable).

Shift tables of changes in clinical significance for the vital signs will be used to assess the changes from baseline to the worst post-baseline cases.

All vital signs, corresponding toxicity grading (if applicable), and corresponding clinical significance (if applicable) collected during the study will be listed for the SA Set, and abnormal values will be flagged.

### 6.7.5 Physical Examination

If applicable, physical examination results will be listed for the SA Set. No summaries on physical examination will be presented.

### 6.7.6 Extent of Exposure and Compliance

All exposure and compliance data will be analyzed based on the SA Set.

#### 6.7.6.1 Exposure to IP

Infusions were to be recorded in the subject e-diary or eCRF.

Protocol Section 6.2.2.2 offers a complete description of the treatment to be administered and the conditions for adjusting subject weekly dose or dosing schedule.

Exposure to IP will be summarized. The following quantities will be reported.

- Duration of treatment
  - Reverse-cumulative duration of prophylactic treatment, specifying how many subjects were treated for ≥4 weeks, ≥12 weeks, ≥26 weeks of prophylaxis
- Number of infusions
  - The total number of infusions administered during the study
  - The number and percentage of all infusions administered, by reason for infusion (prophylaxis, bleeding episode, PK evaluation, maintain hemostasis, surgery)
  - The total number of infusions per subject administered during the study
  - The total number of infusions per subject administered for bleeding episodes during the study
  - The total number of infusions per subject administered for maintaining hemostasis
  - The total number of infusions per subject administered for minor surgeries during the study
  - The total number of prophylactic infusions per subject administered during the study
- Amount of ADYNOVATE (IU or IU/kg) used during the study
  - Total consumption of IP (IU or IU/kg) administered to subjects during the study, for overall and by reason for infusion
  - Total consumption of IP (IU or IU/kg) administered to subjects during the study per week and per month.

- Exposure to ADYNOVATE to treat bleeding episodes
  - The number of infusions administered per treated bleeding episode for overall and by type of bleeding episode (spontaneous, injury, and other if applicable)
  - The total dose of ADYNOVATE in IU/kg per subject per treated bleeding episode for overall and by type of bleeding episode (spontaneous, injury, and other if applicable)
- Exposure days (EDs)
  - Total number of EDs for prophylactic treatment per subject
  - Total number of EDs for bleeding episodes per subject
  - Total number of EDs for minor surgeries per subject

**Related Definitions and Derivations**

- Duration of the study: duration for the study for each subject will be calculated as (date of completion/termination – date of informed consent + 1)
- Duration of treatment: duration of treatment for each subject will be calculated as (date of last dose – date of first dose + 1)
- Duration in weeks = duration (days) / 7
- Duration in months = 12 × duration (days) /365.25
- Duration in years = duration (days) /365.25
- Total number of infusions per subject: all unique infusions of ADYNOVATE which are administered between the dates of informed consent and termination from the study, inclusive.
- Total Dose (IU/kg) Per Subject: (1) weight-adjusted dose per infusion will be calculated by the number of units of ADYNOVATE infused (IU) per infusion divided by the last available body weight (kg) prior to the infusion; (2) sum of all weight-adjusted dose per infusion during the study for each subject.
- Average dose per bleeding episode: defined as the sum of all doses (IU/kg or IU as applicable) given to treat bleeding episodes, divided by the number of unique bleeds recorded during the study for each subject.



Exposure parameters listed above will be summarized using descriptive analysis.
Exposure parameters will be summarized by subjects with total EDs < 50, total EDs ⩾ 50, and overall.
A listing will be created, by subject number and visit, giving the date and time of dose administration.

6.7.6.2 Treatment Compliance

The compliance will be calculated based on the following criteria.

- For prophylaxis: an infusion interval of 5 or more days did not occur more than 3 times, a daily dose below 35 IU/kg in no more than 10% of the infusions, and a daily dose above 55 IU/kg in no more than 80 IU/kg but not exceeding plasmatic FVIII peak levels of 200% for subjects receiving prophylactic treatment at any time to ensure patient safety is adequately managed.

- For treatment of bleeding episodes: the dose to treat a bleeding episode was below 5 IU/kg for a minor bleeding episode, below 10 IU/kg for moderate bleeding episode, or below 25 IU/kg for a major bleeding episode for no more than 5 bleeding episodes.

The treatment compliance will be summarized with number (%) of subjects who meet compliance criteria for both FAS and SA Set if different.

## 6.8 Pharmacokinetic, Pharmacodynamic, and Biomarker Analyses

### 6.8.1 Pharmacokinetic Analysis

The analysis of PK will be performed based on PKFAS and PKAS, unless otherwise specified. The analysis of Factor VIII activity will be performed based on SA set and PKFAS. The analysis of IR will be performed based on SA set.

Pharmacokinetic parameters will be estimated for FVIII activity measured by the 1-stage clotting assay following an initial single dose and multiple doses of ADYNOVATE. Pharmacokinetic parameters, as appropriate but not limited to, will include CL (clearance), V (volume of distribution), AUC (area under the concentration versus time curve between defined timepoints), $C_{max}$ (maximum concentration), $C_{predose}$ (predose concentration), elimination-phase $T_{1/2}$, andIR (incremental recovery). For more details, please refer to CPAP and its amendment.

Factor VIII activity (1-stage clotting assay) in PK samples collected following single-dose and multiple dose PK assessments using nominal timepoints, predose and postdose FVIII activity and VWF antigen level will be tabulated and summarized descriptively.

A subject listing of individual PK parameters by visit will be provided for PKAS.



### 6.8.2 Pharmacodynamic Analysis

Not applicable.

### 6.8.3 Biomarker Analysis

Not applicable.

## 6.9 Patient Reported Outcomes (PROs) and Health Care Utilization Endpoints Analysis

### 6.9.1 PRO Analysis

#### 6.9.1.1 EQ-5D-5L

Each question in the EQ-5D-5L will be presented; no derived scores or imputations are required. The change from baseline in EQ-5D-5L item scores will be calculated as the post-baseline visit value minus the baseline value. Descriptive statistics for the item scores and changes from baseline will be estimated using the Hodges-Lehmann estimator.

### 6.9.2 Health Care Resource Utilization Analysis

Healthcare resource utilization (HRU) is collected at each study visit, including:

- Number and duration of hospitalizations
- Number of emergency room visits
- Number of acute care visits
- Number of days missed from school or work

Subjects who answered "No" to questions should be counted as having answered "0" to the questions for collecting numbers for HRU outcome data. Annualized rates (per subject) for the number of hospitalizations, emergency room visits, acute care visits, and days missed from school or work will be calculated as *the number of events* / [*treatment period* (days) / 365.25].

HRU data will also be listed.

## 6.10 Interim Analyses

No interim analysis is planned for this study.

## 6.11 Data Monitoring Committee/Internal Review Committee

No data monitoring committee is planned for this study



## 7.0 REFERENCES

Björkman S et al. (2012). Population pharmacokinetics of recombinant factor VIII: the relationships of pharmacokinetics to age and body weight. Blood; 119(2): 612-618.

SAS Institute Inc. (2017). Base SAS® 9.4 Procedures Guide, Seventh Edition. Cary, NC: SAS Institute Inc.

SAS Institute Inc. (2017). SAS/STAT® 14.3 User's Guide. Cary, NC: SAS Institute Inc.

FDA Guideline: Guidance for Industry of Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials (September 2007).

## 8.0 CHANGES TO PROTOCOL PLANNED ANALYSES

- An additional analysis set, "Screened Set", is defined in to include all subjects who sign the ICF.

# 9.0 APPENDIX

## 9.1 Changes From the Previous Version of the SAP

Changes made from the previous version of the SAP that have a material impact to the planned statistical analysis methods are described below. In addition, there were textual changes purely to improve the flow, organization and clarity. As these represent cosmetic changes with no impact to the planned statistical analyses, they are not included in the table below.

| SAP Section | Impacted Text (shown in bold) | Change | Rationale for Change |
|---|---|---|---|
| 6.6.3 Subgroup Analyses | **The following endpoint will be summarized in the subgroup of evaluable subjects…** | Added subgroup analyses for evaluable subjects | To show related efficacy results for the evaluable subjects |
| 6.8.3 Biomarker Analysis | The entire section | The entire section removed | To update SAP to be consistent with Protocol Amendment 1 |
| 6.9.1.1 Haemo-SYM Questionnaire | The entire section | The entire section removed | To update SAP to be consistent with Protocol Amendment 1 |
| 6.9.2 Health Care Resource Utilization Analysis | The entire section | Update the descriptions for analyses | To update SAP to be consistent with Protocol Amendment 1 |



## 9.2 Data Handling Conventions

### 9.2.1 General Data Reporting Conventions

All subject data that are collected during this study will be disclosed on listings. Listings will be sorted by subject number, unless otherwise specified. In general, imputed data will not be shown on listings. If imputed values must be shown on a listing to ensure traceability or clarity of the statistical methods, these values will be clearly identified on the output.

Where applicable, variables will be summarized descriptively by study visit.

In general, means and medians will be presented to 1 more decimal place than the recorded data. The standard deviations (SDs) will be presented to 2 more decimal places than the recorded data. CIs intervals will be presented using the same number of decimal places as the parameter estimate. Percentages will be presented with 2 decimal places and their 95% CIs 3 decimal places.

In each table with categorical measures, a footnote will be included to identify the denominator used to calculate any percentages. Any cell count of zero will be presented as '0'; the associated percentage of '(0.0%)' will not be presented. Any cell percentage of 100% will be presented without decimals.

All PK concentrations/activities will be reported and analyzed according to the Clinical Pharmacology Analysis Plan (CPAP) (including any amendments). Other unspecified PK

concentrations/activities will be reported and analyzed with the same precision as the source data provided by the bioanalytical laboratory regardless of how many significant figures or decimals the data carry. Unrounded derived PK data will be considered the source data for the calculation of descriptive statistics. Derived PK parameters will be rounded for reporting purposes in by-subject listings. For most derived PK parameters, 3 significant digits will be used as the standard rounding procedure, with the following exceptions:

- Parameters directly derived from source data (e.g., $C_{max}$) will be reported and analyzed using the same precision as the source data.
- Parameters derived from actual elapsed sample collection times (e.g., $t_{max}$) will be reported with the same precision as the actual elapsed sampling time value of the source data.

For the reporting of descriptive statistics for PK data unspecified in the CPAP, the mean, geometric mean, median, SD and CIs will be presented to 1 digit more precision. The minimum and maximum will be presented to the same precision. Coefficient of variation (CV%) and geometric CV (%) will always be reported to 1 decimal place.

Unscheduled assessments (i.e., not done at a planned visit) will not be used for time point specific summaries but will be used in tabulation of abnormalities or toxicities.

Data such as (but not limited to) laboratory tests that were not specified for collection in the protocol will be reviewed on a case-by-case basis for handling decisions during the study. Full documentation of data related to subject safety will be the primary consideration in establishing how such data will be handled.

Data points which appear to be spurious (e.g., outliers, values incompatible with life) will be queried and either corrected or explained, if possible. Outliers will not be excluded from, or identified in, any analysis unless otherwise specified. Any data points that are specified for exclusion will be documented in table footnotes or cross-referenced to an appropriate listing.



### 9.2.2 Handling of Missing Data

In general, missing data will not be imputed for any variables, unless otherwise specified.

- Missing Date of IP

  If a subject has a missing or partial date of first administration of IP, then the first dose date will be imputed as the earliest dispensing date of IP. When applicable, the imputed first dose date will be used for deriving study days, treatment emergence, prior/concomitant status and time to event endpoints.

  When the date of the last dose of IP is missing for a subject in the SA Set, all efforts will be made to obtain the date from the investigator. If it is still missing after all efforts, then the date of last dose will be imputed as the date of the last visit when IP was returned. The imputed date will be used to calculate treatment duration.

If required for an analysis, any other missing or incomplete date of IP administration will be imputed as the date closest to the planned administration date which is consistent with the available data.

- Missing Date Information for Prior/Concomitant Medications

  Incomplete Start Date

  For prior or concomitant medications and/or non-drug therapies/procedures, incomplete (i.e., partially missing) start date and/or stop date will be imputed. When the start date and the stop date are both incomplete for a subject, impute the start date first.

- Missing Day, Month, and Year

  The start date will be imputed as the date of first dose of IP in the study.

- Missing Day and Month

  If the year of the incomplete start date is the same as the year of the date of the first dose of IP, then the day and month of the date of the first dose of IP will be assigned to the missing fields

  If the year of the incomplete start date is before the year of the date of the first dose of IP, then 31 December will be assigned to the missing fields

  If the year of the incomplete start date is after the year of the date of the first dose of IP, then 01 January will be assigned to the missing fields

  - Missing Month only

    The day will be treated as missing and both month and day will be replaced according to the above procedure

  - Missing Day Only

    If the month and year of the incomplete start date are the same as the month and year of the date of the first dose of IP, then the day of the date of the first dose of IP will be assigned to the missing day

    If either the year is before the year of the date of the first dose of IP, or if both years are the same but the month is before the month of the date of the first dose of IP, then the last day of the month will be assigned to the missing day

    If either the year is after the year of the date of the first dose of IP, or if both years are the same but the month is after the month of the date of the first dose of IP, then the first day of the month will be assigned to the missing day

  Incomplete Stop Date

  - Missing Day, Month, and Year

    The end date will be interpreted as "ongoing" and no date will be imputed.

- Missing Day and Month

  If the year of the incomplete stop date is the same as the year as of the date of the last dose of IP, then the day and month of the date of the last dose of IP will be assigned to the missing fields

  If the year of the incomplete stop date is before the year of the date of the last dose of IP, then 31 December will be assigned to the missing fields

  If the year of the incomplete stop date is after the year of the date of the last dose of IP, then 01 January will be assigned to the missing fields

- Missing Month Only

  The day will be treated as missing and both month and day will be replaced according to the above procedure

- Missing Day Only

  If the month and year of the incomplete stop date are the same as the month and year of the date of the last dose of IP, then the day of the date of the last dose of IP will be assigned to the missing day

  If either the year is before the year of the date of the last dose of IP, or if both years are the same but the month is before the month of the date of the last dose of IP, then the last day of the month will be assigned to the missing day

  If either the year is after the year of the last dose of IP, or if both years are the same but the month is after the month of the date of the last dose of IP, then the first day of the month will be assigned to the missing day



- Missing Date Information for Adverse Events

  AEs with completely missing start dates will be considered TEAE, and AEs with completely missing stop dates will be considered ongoing.

  For AEs with partial end dates, no imputation will be made, and no duration will be calculated.

  For AEs with partial start dates, the non-missing date parts and the investigator's report regarding the relationship of AE onset to IP will be used to determine if the AE is treatment-emergent or not. If a determination cannot be made using the non-missing date parts, then the AE will be classified as treatment-emergent.

  The imputation rules for a partial start date described in the previous section will be used.

- Missing Seriousness

  Events of unknown seriousness will be tabulated as SAE's in the final analysis; however, every effort will be made to avoid data lock with events for which a determination of

seriousness remains missing. The Medical Monitoring Plan presents details of how this effort will be executed.

- Missing Severity Assessment for Adverse Events

  If severity is missing for an AE starting prior to the date of the first dose of IP, then a severity of "Mild" will be assumed. If the severity is missing for an AE starting on or after the date of the first dose of IP, then a severity will be assigned as follows.

  - If a subject experiences more than one AE categorized under the same preferred term, where one of them is categorized as "severe" and one of them is categorized as missing, then the maximum severity for this preferred term should be counted as "severe" for this subject
  - If a subject experiences more than one AE categorized under the same preferred term, one of them is categorized as "mild" or "moderate" and one of them is categorized as missing, then the maximum severity for this preferred term should be counted in most severe grade available in the same PT for this subject.

- Missing Relationship to IP for Adverse Events

  If the relationship to IP is missing for an AE starting on or after the date of the first dose of IP, a causality of "Related" will be assigned.

  Both the actual and the imputed values will be included in data listings.

- Character Values of Clinical Laboratory Variables

  Laboratory measurements will be presented in SI units, unless otherwise specified for an analysis. If a laboratory result is expected to have a numeric value, but the data which are received include a special character such as ">" or "<", then the result will be assumed to lie outside the range of quantitation.

  Any non-PK quantitative laboratory measurement reported as "<X", i.e., below the limit of quantification (BLQ), or ">X", i.e., above the upper limit of quantification will be presented as recorded, i.e., as "<X" or ">X" in listings. All safety laboratory results recorded as "<X" or ">X" will be summarized using the numerical part of the value ("X").



### 9.2.3 Definition of Baseline

In general, baseline will be defined as the last observed value prior to taking the first dose of IP (based date/times), or on the same day on taking the first dose of IP (based on dates), unless otherwise specified.

### 9.2.4 Definition of Visit Windows

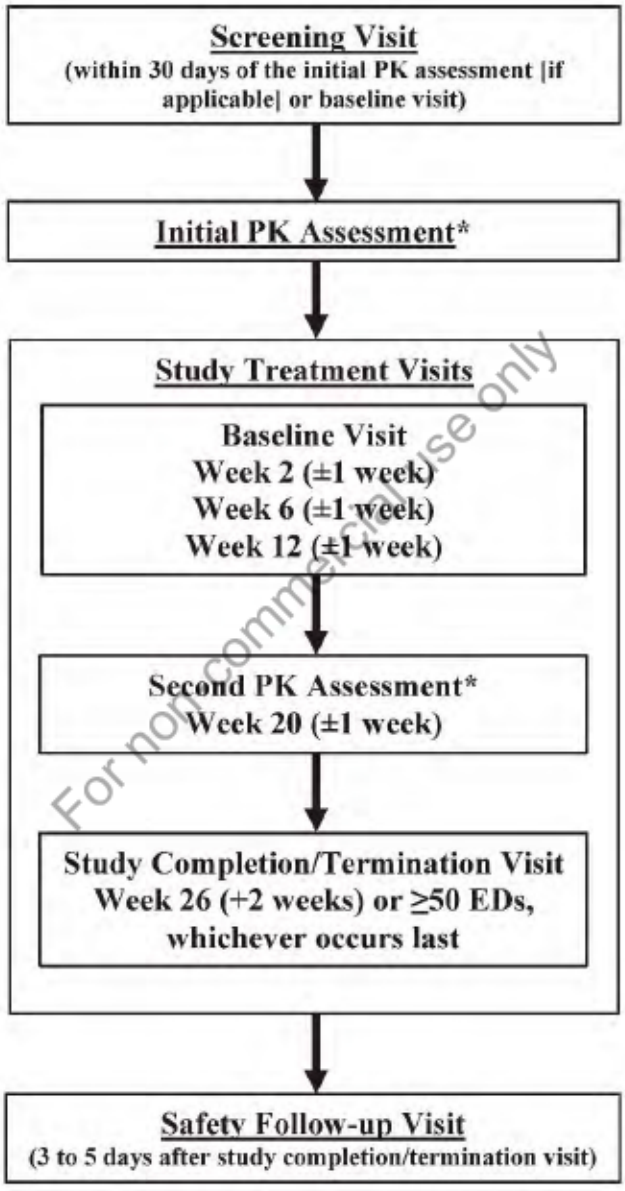
Visit windows are not required for the analysis of the study.

### 9.3 Analysis Software

All analyses will be conducted using SAS® (SAS Institute Inc) software package, version 9.4 or later.

## 9.4 Schema

**Figure 1. Study Schematic Diagram**




ED=exposure day; PK=pharmacokinetic
* Only for subjects who undergo the PK assessments

## 9.5 Schedule of Activities

**Table 2. Schedule of Activities**

| Procedures/ Assessments | Screening Visit [a] | Initial PK Assessment [b] | | | Study Treatment Visits | | | | | | | | Safety Follow-up Visit [d] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | Second PK Assessment [b] | | | Study Completion/ Termination Visit | |
| | Within 30 days | Preinfusion | Infusion | Postinfusion | Baseline Visit | Week 2 (±1 week) | Week 6 (±1 week) | Week 12 (±1 week) | Week 20 (±1 week) Preinfusion | Week 20 (±1 week) Infusion | Week 20 (±1 week) Postinfusion | Week 26 (+2 weeks) or ≥50 EDs [c], whichever occurs last | |
| Informed Consent/ Assent [e] | X | | | | | | | | | | | | |
| Demographics | X | | | | | | | | | | | | |
| Eligibility Criteria | X | | | | | | | | | | | | |
| Medical/ Medication History [f] | X | | | | | | | | | | | | |
| Concomitant Medication [g] | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Adverse Events [g] | X | X | X | X | X | X | X | X | X | X | X | X | X |

**Table 2. Schedule of Activities**

| Procedures/ Assessments | Screening Visit [a] | Initial PK Assessment [b] | | | Study Treatment Visits | | | | | | | | Safety Follow-up Visit [d] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | Second PK Assessment [b] | | | Study Completion/ Termination Visit | |
| | Within 30 days | Preinfusion | Infusion | Postinfusion | Baseline Visit | Week 2 (±1 week) | Week 6 (±1 week) | Week 12 (±1 week) | Week 20 (±1 week) Preinfusion | Week 20 (±1 week) Infusion | Week 20 (±1 week) Postinfusion | Week 26 (+2 weeks) or ≥50 EDs [c], whichever occurs last | |
| Bleeding Episodes and Treatment [g] | X | X | X | X | X | X | X | X | X | X | X | X | |
| Physical Examination [h] | X | X | | | X | X | X | X | X | | | X | |
| Vital Signs [i] | X | X | | X | X | X | X | X | X | | X | X | |
| Clinical Laboratory Assessments [j] | X | X | | X | X | X | X | X | X | | X | X | |
| Subject eDiary [k] | | X [l] | | | X [l] | X | X | X | X | | | X | |
| ePRO Assessments [m] | | X [l] | | | X [l] | | | | | | | X | |

**Table 2. Schedule of Activities**

| Procedures/ Assessments | Screening Visit [a] | Initial PK Assessment [b] | | | Study Treatment Visits | | | | | | | | Safety Follow-up Visit [d] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | Second PK Assessment [b] | | | Study Completion/ Termination Visit | |
| | Within 30 days | Preinfusion | Infusion | Postinfusion | Baseline Visit | Week 2 (±1 week) | Week 6 (±1 week) | Week 12 (±1 week) | Week 20 (±1 week) Preinfusion | Week 20 (±1 week) Infusion | Week 20 (±1 week) Postinfusion | Week 26 (+2 weeks) or ≥50 EDs [c], whichever occurs last | |
| Healthcare Resource Utilization [n] | | | | | X | X | X | X | X | | | X | |
| IP Treatment [o] | | | X | | X | X | X | X | | X | | X | |
| IP Dispensation | | | | | X | X | X | X | | | X | | |
| Investigator Assessment of Hemostatic Efficacy [p] | | | | | X | X | X | X | | | | X | |
| IR Assessments [q] | | | | | X | | X [r] | | | | | X | |

ABR=annualized bleeding rate; AE=adverse event; EC=ethics committee; eCRF=electronic case report form; ED=exposure day; eDiary=electronic diary; ePRO=electronic patient-reported outcome; FVIII=factor VIII; IP=investigational product; IR=incremental recovery; PK=pharmacokinetic(s); PRO=patient-reported outcome

[a] The screening visit procedures, including laboratory evaluations, are to be completed within 30 days prior to the initial PK assessment procedures (if applicable) or baseline visit. At least 72 to 96 hours must have elapsed since the subject's last FVIII therapy (on-demand or prophylactic), if applicable, and the subject must not be actively bleeding.

[b] For subjects participating in the PK portion of the study, the initial PK assessment will be conducted after a washout period of at least 72 to 96 hours following their last FVIII therapy (if applicable) and prior to baseline visit. The second PK assessment will be performed following the scheduled prophylactic treatment dose. The PK samplings for both the initial and second PK assessments should be taken following the time points listed in Table 4. The PK blood samples collected for PK assessments will be measured for FVIII activity (1-stage clotting assay). Subjects undergoing PK evaluation will enter the prophylactic treatment phase 96 hours (±4 hours) after the initial PK infusion.

[c] Exposure day calculation starts from the first PK infusion or baseline visit and completes at study completion/termination visit.

[d] The study site will follow up via phone call with each subject 3 to 5 days after the last ADYNOVATE infusion for the occurrence of AEs.

[e] Written informed consent/assent must be obtained prior to any study-specific procedure.

[f] Medical history will include immunization history, surgery history, hemophilia history, bleeding episode history, and history of FVIII usage over the last year. Target joints and subject's ABR based on the previous 9 to 12 months will also be recorded. Medication history will include the name of the product, dose, dosing interval, and regimen start and end date.

[g] Concomitant medications, nondrug therapies, AEs, bleeding episodes, and their treatment will be continuously monitored by the study site and reviewed and discussed with the subject at study visits.

[h] Physical examination will include, at a minimum, assessments of the general appearance, head and neck, eyes and ears, nose and throat, chest, lungs, heart, abdomen, extremities and joints, lymph nodes, skin, and neurological.

[i] Vital signs include height (only at screening), weight, body temperature, respiratory rate, pulse rate, and blood pressure taken following 15 minutes of rest. The time points for pre- and postinfusion measurements are: within 30 minutes before infusion start (prior to blood sample collection) and 30±15 minutes post infusion. Weight is measured preinfusion only.

[j] At all laboratory assessments, subjects must not be actively bleeding. Assessments should only be performed after a washout period of at least 72 to 96 hours following the last infusion of any other nonmodified FVIII concentrate and 84 to 96 hours following the last infusion of ADYNOVATE. In addition to the assessments shown, clinical laboratory assessments should be performed whenever clinically indicated. For more detailed information, please see Table 3.

[k] The eDiary will be dispensed after subject eligibility is confirmed and before first dose. eDiaries will be completed before each site visit and reviewed by the investigator during the visit. The investigator will check the eDiary for completeness and request missing information periodically, at a minimum at each subject visit, and in a timely manner.

[l] For subjects participating in the PK portion of the study, the first eDiary/PRO assessment should be completed prior to the initial PK assessment. For subjects not undergoing PK assessment, the first eDiary/PRO assessment should be completed prior to baseline visit.

[m] The PRO assessment, using the EQ-5D-5L, will be captured via an ePRO device dispensed after subject eligibility is confirmed and before the first dose. The EQ-5D-5L is to be completed before specified study visits and reviewed by the investigator during the visit.

[n] Healthcare resource utilization evaluation, including number and duration of hospitalizations, number of emergency room visits, number of acute care visits, and number of days missed from school/work will be gathered by the sites via questionnaire as part of the eCRF.

[o] ADYNOVATE is administered at the study site for all study-required visits. Whenever possible, the IP treatment at the study site shall be in accordance with the subject's twice-weekly ADYNOVATE prophylactic treatment regimen. All other study treatments may be administered either at a clinic/hospital/study site or at home by self-administration/administration by a parent/caregiver. The investigator will determine the setting of treatment administration.

[p] Efficacy of ADYNOVATE treatment will be assessed using a 4-point efficacy rating scale (See Protocol Table 7).

[q] Incremental recovery will be calculated by the investigator. Blood samples should be taken within 30 minutes before ADYNOVATE administration and 30±10 minutes post ADYNOVATE infusion. The IR determination at baseline visit will only be performed in subjects who have not undergone the initial PK assessment.

[r] Incremental recovery over time during prophylactic treatment will be evaluated at ED1, Week 6, and ED50. If possible, the Week 6 visit should evaluate ED10 to ED15.

**Table 3. Clinical Laboratory Assessments**

| Procedures/ Assessments | Screening Visit [a] | Initial PK Assessment [b] | | | Study Treatment Visits | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | Second PK Assessment [b] | | | Study Completion/ Termination Visit |
| | Within 30 days | Preinfusion | Infusion | Postinfusion | Baseline Visit | Week 2 (±1 week) | Week 6 (±1 week) | Week 12 (±1 week) | Week 20 (±1 week) Preinfusion | Week 20 (±1 week) Infusion | Week 20 (±1 week) Postinfusion | Week 26 (+2 weeks) or ≥50 EDs [c], whichever occurs last |
| Immunology [d] | X | | | | | | | | | | | |
| Blood Type [e] | X | | | | | | | | | | | |
| Hematology [f] | X | | | | X | | | X | | | | X |
| Clinical Chemistry [g] | X | | | | X | | | X | | | | X |
| Immunogenicity [h] | X | | | | X | X | X | X | | | | X |
| FVIII Activity [i] | X | X [j] | | | X [k] | X | X [k] | X | X | | | X [k] |
| FVIII/VWF Antigen [i] | X | X [j] | | | X | X | X | X | X | | | X |
| Coagulation Function [l] | X | | | | | | | | | | | |

**Table 3. Clinical Laboratory Assessments**

| Procedures/ Assessments | Screening Visit [a] | Initial PK Assessment [b] | | | Study Treatment Visits | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | Second PK Assessment [b] | | | Study Completion/ Termination Visit | |
| | Within 30 days | Preinfusion | Infusion | Postinfusion | Baseline Visit | Week 2 (±1 week) | Week 6 (±1 week) | Week 12 (±1 week) | Week 20 (±1 week) | | | Week 26 (+2 weeks) or ≥50 EDs [c], whichever occurs last | |
| | | | | | | | | | Preinfusion | Infusion | Postinfusion | | |
| Pharmacokinetic Test [m] | | X | | X | | | | | X | | X | | |

ALP=alkaline phosphatase; ALT=alanine aminotransferase; aPTT=activated partial thromboplastin time; AST=aspartate aminotransferase; BU=Bethesda unit(s); BUN=blood urea nitrogen; CHO=Chinese hamster ovary; eCRF=electronic case report form; ED=exposure day; FVIII=factor VIII; GGT=gamma-glutamyl transferase; HbcAb=hepatitis B core antibody; HbsAb=hepatitis B surface antibody; HbsAg=hepatitis B surface antigen; HCV=hepatitis C virus; HIV=human immunodeficiency virus; INR= international normalized ratio; IR=incremental recovery; PK=pharmacokinetic(s); VWF=von Willebrand factor.

[a] The screening visit procedures, including laboratory evaluations, are to be completed within 30 days prior to the initial PK assessment procedures (if applicable) or baseline visit.

[b] For subjects participating in the PK portion of the study, the initial PK assessment will be conducted after a washout period of at least 72 to 96 hours following their last FVIII therapy (if applicable) and prior to baseline visit. The second PK assessment will be performed following the scheduled prophylactic treatment dose. The PK samplings for both initial and second PK assessments should be taken following the time points listed in Table 4. The PK blood samples will be measured for FVIII activity (1-stage clotting assay).

[c] Exposure day calculation starts from the first PK infusion or baseline visit and completes at study completion/termination visit.

[d] Immunology assessments will include HIV-1/HIV-2 antibody, HbsAg, HbsAb, HbcAb, and HCV antibodies. The HCV titer will be confirmed by polymerase chain reaction for all subjects reported as HCV-positive. If a subject is HIV-positive, CD4 count is measured to determine the subject's eligibility.

[e] If historical data on blood group type are available, this may be recorded in the eCRF and blood type does not need to be determined. For subjects who do not have documentation of their blood type in their medical record, ABO blood type will be measured locally at screening.

[f] The hematology panel will consist of complete blood count: hemoglobin, hematocrit, erythrocytes (ie, red blood cell count), leukocytes (ie, white blood cell count) with differential (ie, basophils, eosinophils, lymphocytes, monocytes, and neutrophils), and platelet count.

[g] Clinical chemistry assessments will include sodium, potassium, chloride, bicarbonate, total protein, albumin, ALT, AST, GGT, bilirubin, ALP, urea/BUN, creatinine, glucose, cholesterol, very low-density lipoprotein, low-density lipoprotein, high-density lipoprotein, and triglycerides.

[h] Immunogenicity assessments will include the measurement of inhibitory antibodies to FVIII and binding antibodies to ADYNOVATE. A minimum washout of 72 to 96 hours is required following the last infusion of any other nonmodified FVIII therapy and 84 to 96 hours following the last infusion of ADYNOVATE. Binding antibodies to CHO protein will be included in immunogenicity assessment only at the screening visit, Week 12, and the completion/termination visit.

[i] The blood sample for FVIII activity and FVIII/VWF antigen tests should be collected preinfusion.

[j] For PK subjects, preinfusion blood draws are performed within 30 minutes prior to infusion, meaning no additional blood draw is needed at the baseline visit for these assessments.

[k] For IR determination: blood samples should be taken within 30 minutes before ADYNOVATE administration and 30±10 minutes post ADYNOVATE infusion. The IR determination at the baseline visit will only be performed in subjects who have not undergone PK assessment.

[l] Coagulation function will be assessed via INR at screening and aPTT, as needed, for surgery.

[m]The samples collected for PK assessments following single- and multiple-dose administrations should be taken following the time points listed in Table 4.

Note: At all laboratory assessments, subjects must not be actively bleeding. Assessments should only be performed after a washout period of at least 72 to 96 hours following the last infusion of any other nonmodified FVIII concentrate and 84 to 96 hours following the last infusion of ADYNOVATE.

**Table 4. Pharmacokinetic Sampling Time Points**

| | Preinfusion | Postinfusion | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | Within 30 min | 30 min (±10 min) | 1 hour (±30 min) | 2 hours (±30 min) | 4 hours (±30 min) | 8 hours (±1 hour) | 12 hours (±1 hour) | 24 hours (± 2 hours) | 48 hours (±4 hours) | 72 hours (±4 hours) | 96 hours (±4 hours) |
| Initial PK Assessment | X | X | X | X | X | X | X | X | X | X | X |
| Second PK Assessment Week 20 (±1 week) | X | X | X | X | X | X | X | X | X | X | X[a] |

PK=pharmacokinetic

[a] Performance of 96-hour sampling is dependent on subject's prophylaxis dosing schedule (ie, subject must be on a 3- to 4-day dosing regimen with 4 days until the next infusion at the time of the second PK assessment).