997HA309

Statistical Analysis Plan

Statistical Analysis Plan

Product Studied: Recombinant, Long-acting Coagulation Factor VIII Fc Fusion Protein (rFVIIIFc)

Protocol Number(s): 997HA309

A Randomized, Open-Label Study to Evaluate the Pharmacokinetics and Safety of Recombinant Factor VIII Fc Fusion Protein (rFVIIIFc; BIIB031) Manufactured at 15K Scale and at Vial Strengths up to 6000 IU in Previously Treated Subjects with Severe Hemophilia A

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LIST OF ABBREVIATIONS

AE	Adverse Event
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
ASA	Acetylsalicylic Acid
AST	Aspartate Aminotransferase
aPTT	activated Partial Thromboplastin Time
AST	Aspartate Aminotransferase
AUC_{inf}	area under the concentration-time curve from time zero to infinity
BMI	Body Mass Index
BU	Bethesda Units
BUN	Blood Urea Nitrogen
CI	Confidence Interval
CL	Clearance
C_{max}	maximum activity
CRF	Case Report Form
dL	Deciliter
DNAUC	Dose Normalized Area Under the Curve
DSMC	Data Safety Monitoring Committee
eCRF	Electronic Case Report Form
ED	Exposure Day
EPD	Electronic Patient Diary
FVIII	Factor VIII
GGT	Gamma Glutamyl Transferase
HBV	Hepatitis B Virus
HCV	Hepatitis C Virus
HIV	Human Immunodeficiency Virus
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IgG	Immunoglobulin G
IgG1	Immunoglobulin G1
IR	Incremental Recovery
IU	International Unit
IV	Intravenous
IXRS	Interactive Voice/Web Response System
kg	Kilogram
MedDRA	Medical Dictionary for Regulatory Activities
MRT	Mean Residence Time
PKAS	Pharmacokinetic Analysis Set
PK	Pharmacokinetic
PK1	Pharmacokinetic assessment 1, with 2K rFVIIIFc
PK2	Pharmacokinetic assessment 2, with 15K rFVIIIFc at baseline
PK3	Pharmacokinetic assessment 3, with 15K rFVIIIFc after 13 weeks of treatment
PT	Prothrombin Time

RBC	Red Blood Cell count
rFVIIIFc	recombinant coagulation Factor VIII Fc fusion protein
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SOC	System Organ Class
TEAE	Treatment-Emergent Adverse Event
$t_{½}$	terminal half-life
V_{ss}	Volume of distribution at Steady State
WBC	White Blood Cell count
WHO	World world Health health Organization organization
2K	2000 liter (i.e., the bioreactor scale for the manufacturing of the drug substance that is ultimately packaged into vials that constitute the finished 2K drug product)
15K	15,000 liter (i.e., the bioreactor scale the manufacturing of the drug substance that is ultimately packaged into vials that constitute the finished 15K drug product)

1. INTRODUCTION

Hemophilia A is an X-chromosome-linked bleeding disorder caused by mutations and/or deletions in the F8 gene resulting in a deficiency of coagulation factor VIII (FVIII) activity [Bolton-Maggs and Pasi 2003; Mannucci and Tuddenham 2001]. The coagulation disorder occurs predominantly in males and affects approximately 1 in 5,000 male births [Skinner 2012]. The severity of disease is characterized by the endogenous level of FVIII measured in the plasma. Severe hemophilia A is defined as a coagulation activity of FVIII in plasma (FVIII:C) level of <1% (<1 IU/dL). Individuals with severe hemophilia A experience frequent bleeding and recurrent spontaneous bleeding into the soft tissue and joints, leading to joint damage and severe disability. Repeated bleeding into muscles and joints, which often begins in early childhood, results in hemophilic arthropathy and irreversible joint damage. Damage can lead to limited mobility of joints, muscle atrophy, and chronic pain [Rodriguez-Merchan 2003].

There is no cure for hemophilia A, so treatment focuses on the replacement of FVIII with the intravenous (IV) administration of FVIII-containing coagulation products to promote clotting. The goal of treatment with FVIII-containing coagulation products is to raise the circulating level of FVIII to the lowest effective level to achieve either resolution of bleeding (on-demand treatment) or prevention of bleeding (prophylactic treatment) [MASAC 2009; WFH 2005]. The frequency of administration of FVIII products varies across patients and is tailored to the patient's clinical status, taking into consideration the type of bleeding episode, frequency of bleeding, and goal of treatment for the subject. The dose of FVIII required also varies and has been based on observations over the years as well as guidelines established by organizations such as the National Hemophilia Foundation of the United States and the World Federation of Hemophilia [WFH 2005].

The purpose of this study is to compare the PK of rFVIIIFc drug product manufactured at the 15K scale with the PK of rFVIIIFc manufactured at the current scale (2K) and to evaluate the safety of 15K rFVIIIFc.
In this study, subjects will have the following PK assessments:

- PK1 assessment with rFVIIIFc manufactured at 2K scale (1000 IU/vial).
- PK2 assessment with rFVIIIFc manufactured at 15K scale (1000 IU/vial or 6000 IU/vial) at baseline.
- PK3 assessment with rFVIIIFc manufactured at 15K scale (1000 IU/vial or 6000 IU/vial) after 13 weeks of treatment with 15K rFVIIIFc.

2. DESCRIPTION OF OBJECTIVES AND ENDPOINTS

2.1. Study Objectives

2.1.1. Primary Objective

The primary objective of the study is to compare the PK of rFVIIIFc manufactured at the current scale of 2000 L (2K) to the PK of rFVIIIFc manufactured at the 15,000 L (15K) scale in previously treated subjects with severe hemophilia A.

2.1.2. Secondary Objectives

The secondary objectives of this study are:

- To characterize the PK of 15K rFVIIIFc at the 15K baseline and after 13 weeks of treatment
- To characterize the PK of 15K rFVIIIFc at 1000 IU/vial and 6000 IU/vial strengths
- To evaluate the safety of 15K rFVIIIFc

2.2. Study Endpoints

2.2.1. Primary Endpoint

The primary endpoint includes the following PK parameters for pharmacokinetic assessment 1 with rFVIIIFc manufactured at 2K scale (PK1) and for pharmacokinetic assessment 2 with rFVIIIFc manufactured at 15K scale (PK2), including:

- area under the concentration-time curve from time zero to infinity (AUC_{inf})
- incremental recovery (IR)

as estimated from the coagulation factor VIII (FVIII) activity data, measured by the one-stage (aPTT) clotting assay.

2.2.2. Secondary Endpoints

The secondary endpoints include the following:

1. PK parameters, including but not limited to AUC_{inf}, IR, the maximum FVIII activity (C_{max}), half-life ($t_{½}$), clearance (CL), volume of distribution at steady state (V_{ss}), and mean residence time (MRT).

PK will be assessed using the one-stage (aPTT) clotting assay and the two-stage chromogenic assay.

PK parameters will be assessed for the following

- 15K rFVIIIFc at the 15K baseline (i.e., at PK2) and after 13 weeks of treatment (at pharmacokinetic assessment 3, with 15K rFVIIIFc [PK3])

- 15K rFVIIIFc at 1000 IU/vial and 6000 IU/vial strengths

- 2K rFVIIIFc (at PK1) and 15K rFVIIIFc (at PK2) [except AUC_{inf} and IR, which are included in the primary endpoint]

In addition to the PK endpoints specified in the protocol AUC_{inf}, IR, , $C_{max,}$ $t_{1/2}$, CL, V_{ss} and MRT, the following PK parameters will also be reported and summarized as measured by the one-stage activated partial thromboplastin time (aPTT) clotting assay: time to C_{max} (T_{max}), first order rate constant associated with the terminal portion of the curve (lambda Z), volume of distribution estimated from the terminal phase (V_z), area under the concentration-time curve to the last measureable timepoint (AUC_{last}), area under the concentration-time curve to infinity (AUC_{inf}), and percentage of AUC_{inf} extrapolated from the last data point to infinity ($\%AUC_{ext}$). All PK parameters will also be assessed using the two-stage chromogenic assay.

2. Development of inhibitors as measured by the Nijmegen-modified Bethesda assay
3. Evaluation of adverse events (AEs) and serious adverse events (SAEs)

3. STUDY DESIGN

3.1. Overall Study Design and Plan

This is an open-label, multicenter, randomized study. A minimum of 16 subjects who are at least 12 years of age and have had at least 150 exposure days (150 EDs) to any FVIII product will complete 3 PK assessments and a 26-week treatment period. One ED is defined as a 24-hour period in which a subject receives 1 or more doses of rFVIIIFc, with the time of the first injection of rFVIIIFc defined as the start of the ED.

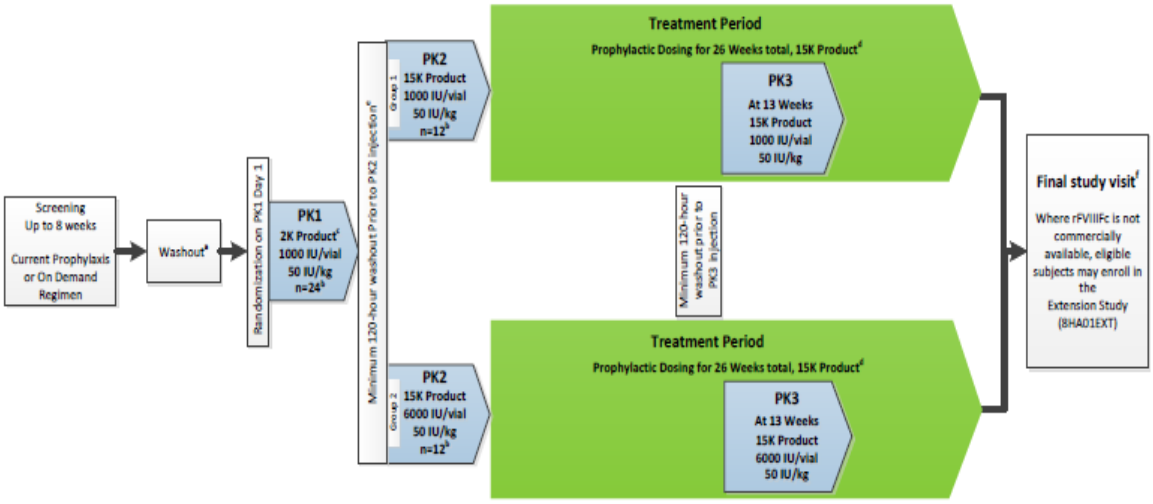
Approximately 24 subjects may be enrolled in order to obtain the necessary number of evaluable subjects as defined in Section 3.5.4.

In this study, subjects will have PK assessments of 2K scale rFVIIIFc at the 1000 IU/vial strength (PK1) followed by PK assessment of either 15K rFVIIIFc at 1000 IU/vial strength or at 6000 IU/vial strength at PK2 (15K baseline) depending on randomization assignment. After 13 weeks of treatment with15K rFVIIIFc (1000 or 6000 IU/vial strength), subjects will be re-evaluated at PK3 using the vials strength to which they were randomized. Following PK3, subjects will continue prophylactic dosing until they reach 26 weeks of treatment with 15K rFVIIIFc (total, starting from the PK2 assessment).

Safety will be assessed over the course of the study. All bleeding episodes and dosing information will be captured in the study diary that the subject (or the subject's caregiver) will maintain throughout the study.

After completion of the study, eligible subjects living in countries where rFVIIIFc is not commercially available will be offered enrollment into extension study 8HA01EXT.
Refer to Figure 1 for a schematic of the study design.

Figure 1: Study Design



Abbreviations: 2K=rFVIIIFc produced at 2000 L scale; 15K=rFVIIIFc produced at 15,000 L scale; PK=Pharmacokinetic sampling period
[a]Minimum of 96 hours of washout for a short-acting FVIII product, or 120 hours of washout for a long-acting FVIII product.
[b]Approximately N=24 subjects may be enrolled in order to complete the study as described in Section 7.5.
[c]If more than 2 bleeds occur during the PK1 assessment period, it will not be rescheduled. The subject may continue on the study in the treatment period.
[d]See Section 10.1.2, for dosing regimens and Section 4.2 for time windows.
[e]The 120-hour washout period for PK2 may begin at the time of the PK1 injection and include the period when the patient is undergoing the PK1 assessment if no additional treatments are needed for bleeds before the PK2 assessment.
[f]There will be a follow up phone call 7 + 7 days after the last dose of rFVIIIFc during the treatment period unless the subject has already enrolled into the extension study, Study 8HA01EXT, by that time.

3.2. Treatment Arms

This is a two-arm PK study

All subjects will have a Follow-Up Telephone Call 7 (+7) days after the last dose of rFVIIIFc during the Treatment Period, unless they have entered directly into extension study 8HA01EXT by that time.

3.2.1. Surgery

For subjects who require emergent or elective surgery during the study period, the dose and regimen of rFVIIIFc will be that deemed appropriate by the Investigator for the type of surgery to be performed, following the guidance in Table 3 section 10.1.4 of the protocol. The definition of minor and major surgery can be found in the same section of the protocol.

All major surgeries will be reported as SAEs.

During surgery and the postoperative period, the following information will be collected:

- number of injections and dose per injection to maintain hemostasis during the surgical period
- estimated blood loss (mL) during surgery and the postoperative period
- number of blood product units transfused during surgery

Bleeding caused directly by surgery should not be reported, although undesired or unexpected bleeding during or after surgery should be recorded on the eCRF.

3.3. Dose Adjustments and Bleeding Episodes

Following the PK2 assessment, subjects will receive prophylactic dosing. The specific choice of regimen for any given subject and any subsequent dose adjustments will be based on the subject's response and will be at the Investigator's discretion.

Recommended starting dosing regimens include the following:

- A prophylactic regimen at a starting dose of 50 IU/kg of rFVIIIFc given every 3 to 5 days. Further dose and interval adjustments will be based on individual clinical response per Investigator's discretion. Dosing may be adjusted in the range of 25 to 65 IU/kg at 3 to 5 day intervals.
- A prophylactic regimen of 65 IU/kg administered every 7 days may be considered for appropriate subjects who will be selected based on the opinion of the Investigator.

Subjects will be allowed to switch from one regimen to another if approved by the Investigator and will be allowed to use any of the several available vial strengths.

If a subject has a bleeding episode during the study, the Investigator should be notified. The Investigator will provide guidance on the dosing for treatment of bleeding episodes as described in Table 2.

Table 2: rFVIIIFc Dosing for Treatment of Bleeding

Severity of Bleed	Desired Peak Factor VIII Level (IU/dL or % of normal)	Dose (IU/kg)/ Frequency of Doses (hrs)
Minor and Moderate For example: joint, superficial muscle/no neurovascular compromise (except iliopsoas), deep laceration and renal. superficial soft tissue, mucous membranes	**40 to 60**	**20 to 30 IU/kg** Repeat every 24-48 hours until bleeding is resolved
Major For example: iliopsoas and deep muscle with neurovascular injury, or substantial blood loss, retroperitoneum, CNS, throat and neck, gastrointestinal	**80 to 100**	**40 to 50 IU/kg** Repeat every 12-24 hours until bleeding is resolved.

Adapted from [WFH 2012].
Subsequent dosage and duration of treatment depends on the individual clinical response, the severity of the factor VIII deficiency, and the location and extent of bleeding.

3.4. Sequence of Enrollment

Subjects will be registered as screened in the Interactive Voice/Web Response System (IXRS) following completion of all screening assessments.

The Screening Period can be extended for subjects who have a bleeding episode requiring treatment with FVIII during the washout period prior to the first injection on Day 1 of PK1 Injection 1.

Once the required washout is complete and all inclusion and exclusion criteria have been met, the subject will be enrolled into the study and randomized.

Discontinued subjects or subjects unable to complete all 3 PK assessments may be replaced if needed to attain the number of subjects required to complete the study as described in Section 3.5.4.

3.5. Number of Subjects

3.5.1. Sample Size

The minimum sample size in this study (16 subjects) is consistent with the EMA guidance for PK assessment of hemophilia products [EMA (EMA/CHMP/BPWP/144533/2009) 2011].

3.5.2. Study Sample

Subject inclusion and exclusion criteria can be found in Sections 8.1 and 8.2 of the protocol.

3.5.3. Procedures for Discontinuing Treatment and Removal of Subjects from the Study

If more than 2 bleeding episodes occur during the PK1 assessment period, the PK assessment will not be rescheduled. However, the subject may continue on the study in the Treatment Period.

Discontinued subjects or subjects unable to complete all 3 PKs may be replaced if needed to attain the number of subjects required to complete the study as described in Section 3.5.4. A subject must permanently discontinue rFVIIIFc treatment and be withdrawn from the study for any of the following reasons:

- A Grade 2 or greater allergic drug reaction occurs in association with administration of rFVIIIFc, as defined below by the Recommendations for Grading of Acute and Sub-Acute Toxic Effects on the World Health Organization (WHO) scale [WHO 1979]:
  - Grade 2 Bronchospasm related to rFVIIIFc; no parenteral therapy needed
  - Grade 3 Bronchospasm related to rFVIIIFc; parenteral therapy required
  - Grade 4 Anaphylaxis related to rFVIIIFc
- An inhibitor is identified and confirmed by a second test conducted at the central laboratory within 2 to 4 weeks of the first positive test using the Nijmegen-modified Bethesda assay.
- Use of FVIII products other than rFVIIIFc occurs, unless it occurs prior to randomization according to the instructions in Table 1 of the protocol, in an emergency and/or as a result of 1 accidental use, and the Sponsor agrees to retain the subject in the study. Use must be recorded in the subject's Study diary and electronic case report form, and the Investigator should contact the Sponsor Medical Monitor.
- The subject withdraws consent.
- The parent or legal guardian withdraws the subject from the study.
- The subject experiences a medical emergency that necessitates permanent discontinuation of study treatment.
- The subject is unwilling or unable to comply with the protocol.
- At the discretion of the Investigator for medical reasons.

The reason for discontinuation of study treatment and withdrawal from the study must be recorded in the subject's eCRF.

Subjects who discontinue treatment should remain in the study to complete protocol required tests and assessments as described in Section 4.2 of the protocol and then must be permanently withdrawn from the study.

3.5.4. End of Study

The study will be considered complete when

- At least 16 subjects (8 in each arm) have evaluable PK data for all three PK assessments AND
- At least 12 subjects have had at least 26 weeks of treatment with 15K rFVIIIFc.

When this occurs, all ongoing subjects will return to the clinic for end-of-study assessments (see Section 4.2.3 of the protocol). End of study will occur when the last subject has had his last visit (Last Subject Last Visit [LSLV]).

3.5.5. Randomization and Blinding

This is an open-label study as such there is no blinding. Subjects will be randomized on Day 1 of PK1 via the IXRS. The randomization will determine their PK2 and PK3 group assignments, to 1 of 2 groups, in a 1:1 ratio. Subjects will receive 1000 IU/vial or 6000 IU/vial of 15K rFVIIIFc.

4. ANALYSIS POPULATIONS

4.1. All-enrolled Analysis Set

The All-enrolled Analysis Set will consist of all subjects who are randomized.

4.2. Safety Analysis Set

The Safety Analysis Set is defined as all subjects who receive at least 1 dose of rFVIIIFc (2K or 15K).

4.3. Full Analysis Set (FAS)

The Full Analysis Set is defined as all subjects who receive at least 1 dose of 15K rFVIIIFc. Subjects who received a dose of 2K rFVIIIFc, but did not receive any 15 K rFVIIIFc will not be included in this population.

4.4. Pharmacokinetic Analysis Set

The Pharmacokinetic Analysis Set (PKAS) is defined as all subjects with evaluable PK profiles. A PK profile for a given injection is considered evaluable if all PK parameters can be determined in at least 1 of the 2 assays and in any PK assessments.

5. DATA HANDLING

This study is being conducted under the sponsorship of Biogen. The data management is being performed under contract with Quintiles in collaboration with Biogen. Statistical analysis is being performed by Biogen, using SAS® version 9.4 or higher and, where appropriate, additional validated software. This statistical analysis plan (SAP) is based on the protocol Version 1.1, dated 21 September 2015, and will detail analyses to be performed and summaries to be produced for the Clinical Study Report (CSR).

5.1. General Principles

The following rules will be followed for all applicable analyses contained in this SAP, unless specified otherwise.

The study day for the start/stop day of events will be calculated from the first dose of rFVIIIFc (for both manufactured scale 2K and 15K) as (date of event – first dose date + 1) if the date of event is on or after the first dose date, or (date of event – first dose date) if the date of event is before the first dose date. That is, Study Day 1 is the first day of treatment with rFVIIIFc (2K or 15K). Study Day -1 is the day immediately preceding Study Day 1. There is no Study Day 0 in this study. For example, if a subject was administered rFVIIIFc (2K) on 01 January 2015 and rFVIIIFc (15K) on 15 January 2015, and an adverse event was recorded with an onset date of 10 January 2015, onset for rFVIIIFc (2K) would be Study Day 10 and for rFVIIIFc (15K) Study Day -5. Study days will be included in the data listings where indicated on the listing shells. 'NA' will be used to indicate that a subject did not receive the respective study drug.

Summaries of the data will be produced using graphs and standard summary statistics. Listings will be provided for all datasets; Datasets and listings will include data collected at unscheduled visits. Data collected at unscheduled visits will be included in the definition of the maximum and minimum post-baseline values, but will not be included in summaries by timepoint or visit unless specified otherwise.

The end-of-study (EOS) visit will be used for the Week 26 summaries only if the visit represents the 26-week time point for the subject.

The principle of last observation carried forward will be utilized for the safety endpoints which are evaluated at study visits. The last observation that is carried forward will be the final evaluation made for a subject. This could represent an unscheduled visit, the EOS visit, any visit prior to the Week 26 visit if the study is ended before all subjects have completed the study, or the Week 26 visit.

Summaries on change from baseline (as defined in Section 5.1.1) by study visit will be based on subjects who have both baseline and post-baseline values at the visit being summarized. Each of the post-baseline timepoint summaries will contain a row that provides the mean baseline value for the subjects included in that visit summary. There will also be a row for the baseline median where indicated on the table shells.

5.1.1. Data Analysis

In the event of repeat assessments at the same timepoint, the last non-missing evaluable measurement will be used for the purpose of analysis. Generally, unscheduled visits will not be included in tables when by-visit summaries are provided.

Except for PK, laboratory values of the form "<x" (i.e., below the lower limit of quantification [LLOQ]) or ">x" (i.e., above the upper limit of quantification [ULOQ] will be imputed as "x" in the calculation of summary statistics but displayed as "<x" or ">x" in the listings. For PK, values <LLOQ will be imputed as 0 and values >ULOQ will be imputed as the ULOQ in the calculation of the descriptive statistics for FVIII activity.

Unless specified otherwise, for the purpose of analyses involving change from baseline during treatment with rFVIIIFc, baseline will be defined as the last non-missing measurement (that can be used for data analysis) taken prior to the first dose of rFVIIIFc. If a subject required rescreening during the study, then baseline characteristics will be taken from the first screening visit.

Except for PK doses, the unit body weight dose (IU/kg) for analysis of dosing will be calculated as the total IU (nominal dose) for each injection divided by the subject's most recent weight in kilograms prior to the dose of study drug. PK doses are all to be administered as 50 IU/kg. The PK scientist will adjust the dose-dependent PK parameters when the actual administered PK dose was not 50 IU/kg; these adjustments will be acknowledged in the final PK parameter tables and listings.

The initial PK dose is not used for the purpose of preventing or treating bleeds and therefore the total annualized rFVIIIFc consumption will exclude the IU/kg amount that was used during the PK period. However, data collected over the time in which the PK dose was administered will be included in the safety analyses.

5.1.2. Handling of Missing Data

Aside from the following, no imputation of study data will be performed. The occurrence of a new bleeding episode will be imputed if >72 hours elapse between 2 consecutive injections administered to treat a bleed. Details are provided in Section 8.1.6.

For the analysis of AEs and concomitant medications/procedures, if the stop/start date of an AE/concomitant medication is missing or partial, the corresponding study day will be left blank. However, inferences will be made from the partial and missing dates to classify medications as prior and/or concomitant and AEs as treatment emergent (or not). These inferences are described in Sections 6.4.1 and 9.2.3, respectively.

5.2. Data Summaries

5.2.1. Continuous Variables

Continuous variables will be summarized using descriptive statistics including the number of non-missing values (n), mean, standard deviation (SD), median, minimum, and maximum. Where specified in the table shells, the 25^{th} and 75^{th} percentiles will also be provided. Pharmacokinetic parameters will also be summarized with the arithmetic mean, geometric mean, 95% confidence intervals on the arithmetic and geometric means, and %CV. Means (arithmetic and geometric), medians, confidence intervals, and the 25^{th} and 75^{th} percentiles will be presented to one decimal place beyond that with which the data was captured. SDs will be presented to

two decimal places beyond that with which the data was captured. Minimum and maximum will be displayed to the same number of decimal places as that with which the data was captured. %CV will be displayed with 1 decimal place for all PK parameters.

Unless impractical within a given table, statistics will be aligned by the decimal place in the summary tables.

5.2.2. Categorical Variables

Categorical variables will be summarized by counts and percentages. All percentages will be rounded to one decimal place. The percentage will be suppressed when the count is zero. Unless specified otherwise, the denominator for all percentages will be the overall number of subjects (or other experimental unit, e.g. bleeding episodes) with non-missing data for a given summarization. This number (n) will be included with categorical summaries unless the same variable is also being summarized with descriptive statistics, in which case 'n' will already be provided. This applies to all categorical summaries except when n=N due to the nature of the data being summarized (e.g., adverse events).

5.3. Study Periods

5.3.1. Screening Period

The screening period starts after signing the study consent form and ends immediately prior to the first dose of rFVIIIFc.

5.3.2. PK Periods

The rFVIIIFc PK1 (2K [PK1] 1000 IU/Vial) profiling period is defined as the period starting at the 2K [PK1] dose of rFVIIIFc and ending 1 minute prior to the first prophylactic (2K or 15K) or 15K PK2 dose.

The rFVIIIFc PK2 (15K [PK2] 1000 and 6000 IU/Vial) profiling period is defined as the period starting at 15K [PK2] dose and ending 1 minute prior to the first prophylactic dose of rFVIIIFc after 15K [PK2] dose .

The rFVIIIFc PK3 (15K [PK3] 1000 and 6000 IU/Vial) profiling period is defined as the period starting at 15K [PK3] dose of rFVIIIFc and ending 1 minute prior to the first prophylactic dose of rFVIIIFc after 15K [PK3] dose.

The pre surgery PK period is defined as the period starting at pre surgery Visit 1 dose of rFVIIIFc and ending 1 minute prior to the first prophylactic dose of rFVIIIFc after the pre surgery PK dose. If there are no prophylactic doses between surgery visit 1 and 2 then the pre surgery PK period will end one minute prior to the collection time of pre dose FVIII activity sample at surgery visit 2.

5.3.3. Treatment Period (Efficacy Period)

During the treatment period that follows PK2; all subjects will receive a minimum of 26 weeks of prophylactic treatment with 15K rFVIIIFc. The treatment period for the evaluation of bleeding and consumption, as well as for measures of compliance, is determined from a combination of dosing dates/times and PK and/or surgical/rehabilitation periods. The treatment period is defined as follows:

- The treatment period starts with the date and time of the first prophylactic dose following a completed rFVIIIFc PK2 sampling period (including a bridging dose if administered (see Section 5.3.2)) and ends with last dose administered (for prophylaxis or a bleed) as recorded in the eCRF or in a handheld electronic patient diary (EPD). That is, if the initial PK2 sampling period is incomplete due to an aborted collection of blood samples following the PK injection (e.g., because of a bleeding episode that required treatment) then the treatment period will begin following a subsequent fully executed PK2 sampling period.
- Subjects who bleed within 72 hours after the rFVIIIFc PK2 dose (i.e., an incomplete PK period): these subjects are to proceed to prophylactic dosing.

The treatment period is interrupted for PK assessments (PK3 or pre surgery PK) and or for all surgical/rehabilitation periods (major and minor), as follows. The treatment period continues up to the last dose (for prophylaxis or a bleed) before the any PK dose or the last dose (for prophylaxis or a bleed) before the start of the surgical/rehabilitation period and then continues at the next prophylactic dose following the end of the PK3, pre surgery PK (see Section 5.3.2) or surgical/rehabilitation period (see Section 5.3.4). The interval of time between the last dose before a PK dose and the PK dose for subjects who undergo surgery, or between the last dose before a surgical/rehabilitation period and the start of the surgical/rehabilitation period for all surgeries will not be attributed to the treatment period. By definition, there should not be any treated bleeding episodes in these intervals of time. Bleeding episodes that occur after the last sample collection for PK but before the next prophylactic dose will be attributed to the PK period and hence not counted towards the annualized bleeding rate. Similarly, bleeding episodes that occur after discharge from a rehabilitation facility but before the next prophylactic dose will be attributed to the surgical/rehabilitation period and hence not counted towards the annualized bleeding rate.

The total duration of time allocated to the treatment period will be calculated in minutes and converted to days as the number of minutes divided by 1440.

All the 2K injections and bleeding episodes that will occur between the PK1 and PK2 will not be considered in the treatment period.

5.3.4. Surgical/Rehabilitation Period

The broadest span of time for the surgical/rehabilitation period is from the first dose of rFVIIIFc given for the surgery (i.e., the pre-surgery dose) up to 1 minute before the first regular prophylactic dose after the last day of postop care/rehabilitation. Since not all subjects will have these events, specific considerations for the start and end of the surgical/rehabilitation period are as follows:

Start of the surgical/rehabilitation period:

- If there is more than one pre-surgical dose then the first one should be selected (a pre-surgical dose can be administered the day before the surgery)
- If there is no pre-surgical dose but there was a prophylaxis dose the day before surgery, this prophylaxis dose should be selected

- If there is no pre-surgical dose or a prophylaxis dose the day before surgery then select the start date/time of the surgery. If the time was not recorded then select the date and impute 00:01 for the time.

End of the surgical/rehabilitation period:

- 1 minute before the first prophylactic dose on or after the last date among the dates for discharge from the hospital, post-operative visit 1, post-operative visit 2, and the end of rehabilitation
- If all of the dates mentioned above are missing, then select the first prophylactic dose after the date/time for the end of surgery. If the surgery time was not recorded then select the surgery date and impute 23:59 for the time. If the end date of the surgery is missing then select the start date of the surgery and impute 23:59 for the time.
- If there are no prophylaxis doses following the latter of the 5 dates mentioned above, then select the latter of the dates and impute 23:59 for the time if otherwise there is no time associated with the given date (eg, the subject completed the surgical/rehabilitation period but received no further prophylactic doses).
- If the overall end of study is declared while the subject is still in the surgical/ rehabilitation period then select the date of the end of study visit and impute 23:59 for the time if a time is not provided.

Three exceptions are noted:

- If 2 (or more) major surgeries are performed without an intervening discharge from the hospital, then the first surgical/rehabilitation period will end 1 minute before the start of the next surgery and the second surgical/rehabilitation will end as described above.
- If minor surgery is performed during postoperative care or rehabilitation then the surgical/rehabilitation period for the minor surgery will start and end on the day of the minor surgery, at 00:01 and 23:59, respectively, if times are not otherwise provided. The surgical/rehabilitation period for the major surgery will include the minor surgery (ie, the surgical/rehabilitation period for the major surgery does not stop and restart around the minor surgery) and will end as otherwise defined.
- If a PK assessment falls within a surgical/rehabilitation period then the PK period is determined as indicated above and removed from the surgical/rehabilitation period (ie, the surgical/rehabilitation period is interrupted by the PK period). This refers to the PK assessments made to determine the PK parameters at the beginning of the study and pre-surgery; it does not apply to the trough and recovery levels obtained at scheduled visits.

Within the total surgical/rehabilitation period, the time is divided into:

- Intraoperative period: from the date/time of the pre-surgery rFVIIIFc dose to the date/time of the end of surgery.

- Postoperative care period: from the date and time plus 1 minute following the end of surgery to the last dose of rFVIIIFc given for the surgery, including doses given to prevent bleeding during the postoperative period.
- Postoperative rehabilitation period: from the date following the last day of postoperative care to the end of the surgical period as described above.

The surgical/rehabilitation period will be determined in the same manner for both major and minor surgeries.

5.3.5. Safety Period

The safety period is defined as the period from the first dose of rFVIIIFc to the last study visit (Week 26 for subjects who continue into the extension study, or the Follow-up telephone call for subjects who do not continue). Events occurring after the start of the first rFVIIIFc PK (PK1) dose up to the second rFVIIIFc PK (PK2) dose will be considered separately from the treatment period of 15K rFVIIIFc treatment (between PK2 and to the last study visit) .

6. STUDY SUBJECTS

6.1. Disposition of Subjects

Subject disposition will be summarized for each PK vial strength (1000 and 6000 IU/vial as per randomization) and overall, for the All-enrolled Analysis Set. This table will present the number and percentage of subjects in the Safety Analysis Set, Full Analysis Set, and subjects with a treatment period, who underwent major surgery; also this table will present the number and percentage of subjects

- with a PK dose for 2K [PK1] and 15K [PK2 and PK3] doses
- In the PKAS population with the number of subjects who have evaluable PK profiles for PK1, PK2 and PK3; for PK1 and /or of PK2 and for PK2 and/ or PK3.
- who completed/discontinued the study, including the primary reason for those who discontinued.

All percentages will be based on the number of subjects in the All-enrolled Analysis Set except for the PK-related evaluable entries which will be based on the number of subjects in the PKAS population. Subject disposition, including the date of the last visit and the reason for early termination for subjects who did not complete the study, will be provided in a data listing.

The overall number and percentage of subjects enrolled will be summarized by country and site for the All-enrolled Analysis Set. The overall number of subjects attending each visit will be summarized by planned visit for the Safety Analysis Set. The summary for Week 26 will include only those subjects for whom the visit evaluations reflect 26 weeks on the study (i.e., excluding subjects for whom this visit represents the end-of-study visit due to early termination).

6.2. Demography and Baseline Disease Characteristics

Demographics and baseline characteristics will be summarized overall for the Safety Analysis Set and for each vial strength and overall for the Pharmacokinetic Analysis Set. Overall baseline disease characteristics, based on the general medical and surgical history, hemophilia history, bleeding history, will be summarized for the Safety Analysis Set.

6.2.1. Demography

Demographic characteristics include age, height, weight, and body mass index (BMI) at screening plus race, ethnicity, and geographic location. Geographic locations are defined as North America, and other. Other countries include Australia (AUS) and New Zealand.

Age will be summarized both as a continuous variable using descriptive statistics and categorically using the following age categories (in years): 12 to 18, 19 to 64 and ≥65. BMI is calculated as weight (kg) / height (m^2). Height, weight, and BMI will be summarized using descriptive statistics.

6.2.2. General Medical and Surgical History

Overall medical and surgical history will be summarized by body system. A subject will be counted only once if they reported more than one occurrence in the same body system. Smoking and alcohol consumption habits will be listed.

6.2.3. Hemophilia History

Categorical summaries will be provided for F8 genotype, types of FVIII product previously administered, and family history of inhibitors. Typical FVIII dosing for minor, moderate, and major bleeds; number of prior exposure days to FVIII; and time since diagnosis of hemophilia will be summarized with descriptive statistics. Hemophilia history will also be summarized categorically for the most recent pre study FVIII regimen (prophylaxis, episodic [on demand]), time on the most recent pre study regimen (<6 months [26 weeks], 6-12 months, >12 months [52 weeks]), and the frequency of injections for subjects who indicated prophylaxis as their most recent pre study regimen. Percentages in the summaries subset by pre study regimen will be based on the number of subjects in the given regimen category who have provided a response to the relevant question. Subjects who reported both a prophylactic and episodic regimen as their most recent regimen (both regimens have identical ending dates) will be included with the prophylactic group.

6.3. Protocol Deviations

All protocol deviations will be recorded throughout the study. Major and minor protocol deviations/violations are to be pre-specified prior to database lock. The Overall number of subjects with major protocol deviations will be summarized by category for the Safety Analysis set.

6.4. Non-study Drug Medications

6.4.1. Prior and Concomitant Medications

The overall prior and concomitant medications relative to rFVIIIFc will be summarized for the Safety Analysis Set. Summaries will be based on the number and percentage of subjects taking medications by WHODRUG standardized medication text. Within each WHODRUG standardized medication text a subject will be counted once even if he reported taking the medication more than once. Separate summaries will be provided for prior and concomitant medications. Medications taken after the Week 26/End of Study (EOS) visit up to the Follow-up visit/phone call will not be included in the summary table of concomitant medications. Two listings will be provided, one for prior and concomitant medications taken through the Week 26/EOS visit and the other for medications taken after the Week 26/EOS visit and prior to the Follow-up visit/phone call.

Medications will be identified as being prior and/or concomitant based on the start and stop dates compared to the first dose of rFVIIIFc. Prior medications are all drugs and substances taken before the first rFVIIIFc dose was received. Concomitant medications are those administered during or after the first injection of rFVIIIFc while on study, or administered prior to the first administration of rFVIIIFc and ongoing at the start of rFVIIIFc administration.

Prior and concomitant medications will be characterized based on the onset and resolution dates relative to the date and time of the first dose of rFVIIIFc. Medications reported for a subject will be classified as concomitant unless they can be excluded as such, as follows:

- A medication that was started prior to the first dose of rFVIIIFc and was ongoing during and/or after the first dose of rFVIIIFc will be classified as both prior and concomitant.

- Medications with a start date after the follow-up visit will not be considered concomitant and will not be included in the summary tables.
- For partial dates, if a concomitant medication start day is missing then the medication will be assumed to be both a prior and a concomitant medication unless the start month and/or year or medication stop date can be used to determine if a medication is concomitant or prior, as follows.
  - If the concomitant medication start day is missing, but the month and year are before the start month and year of the first dose of rFVIIIFc and the concomitant medication stop date is before the start day of the first dose of rFVIIIFc, then the medication will be classed as prior only.
  - If the day of the start date is missing and the month and year are after the month and year of the first dose of rFVIIIFc then the medication will be classed as concomitant only.
  - If the month of the start date is missing and the year is before the start year of the first dose of rFVIIIFc and the stop date is before the start date of the first dose of rFVIIIFc, then the medication will be classed as prior only.

Prior and concomitant medication will be coded using World Health Organization drug enhanced dictionary version June 2015.

6.4.2. Other Therapies and Procedures

Other therapies administered and concomitant procedures performed within 30 days prior to the first dose of study drug through the end of the study will be listed only, a summary table is not planned.

6.5. Study Drug

Study treatment is described in Section 3.2. The listing of all study drug administered will include the reason for (prophylaxis [regular or additional], treatment of a bleeding episode, surgery, other), date and time of administration, dose, and dosing intervals. Treatment with study drug will be listed, including average weekly prophylactic dose, average prophylactic dosing interval, and consumption.

6.5.1. Exposure

6.5.1.1. Number of Injections and Exposure Days to rFVIIIFc

For any subject, the total number of days of exposure to 2K and 15K rFVIIIFc will be calculated separately. The exposure will be accumulated from the time of their first on-study injection of 2K/15K rFVIIIFc, including the rFVIIIFc PK dose when administered. An exposure day (ED) is a 24-hour period in which one or more rFVIIIFc injections are given. The 24-hour window starts from the first injection on study and then for subsequent injections, it starts from an injection taken after/outside of a previously identified ED.

The total number of EDs on 15K rFVIIIFc for each subject will be summarized with descriptive statistics. The Overall total number of 15K rFVIIIFc injections per subject will be summarized

overall and by reason for injection (prophylaxis, spontaneous bleed, traumatic bleed, follow-up injection, surgical, or other) using descriptive statistics for the Full Analysis Set.

6.5.1.2. Duration of rFVIIIFc Dosing

The duration of 15K rFVIIIFc dosing will begin from the first 15K rFVIIIFc dose (PK or prophylaxis) and end with the last 15K rFVIIIFc dose, regardless of the reason for the last dose (e.g. prophylaxis, to treat a bleeding episode, surgical). Duration will be calculated as the date of the last dose minus the date of the first dose +1. Any interruptions to dosing will be ignored for the purposes of calculating the interval. The number and percentage of subjects whose duration of dosing was at least 13 weeks and at least 26 weeks will be tabulated based on the integer part of the calculated week.

This table will also be presented by subgroup based upon contemporaneous entry compliance (<80% and ≥80%) as described in Section 10.

6.5.2. Surgery

Due to the small overall size anticipated for the surgery, the assessments will be derived from subject data listings; summary tables are not planned.

The following information will be provided in the data listings:

- Dates/times for the various components of the surgical rehabilitation period (hospital admission, surgery, discharge)
- The surgical procedure performed, blood loss, drainage
- Blood products used including details for type of transfusion, date/time administered, and amount given
- Dosing during surgery, on the day of surgery, and for the first 14 days post surgery (Days 1-3, Days 4-14, and Days 1-14)
  - during surgery: number of injections, average dose per injection, and total dose required to maintain hemostasis
  - day of surgery: total dose required to maintain hemostasis
  - post-surgery: total rFVIIIFc administered, the total number of injections, and the minimum and maximum intervals of time between injections
- The number of injections required to maintain hemostasis and average daily dose on the day of surgery and for Days 1-3 and Days 4-14 following surgery
- Injections and bleeding episodes during surgery and for the first 14 days following surgery, FVIII levels, reason for injection, nominal dose, hours since the last injection, and if any additional treatment was given to treat the bleed

During surgery includes the loading dose given for the surgery. The day of surgery refers to the calendar day of the surgery and includes the loading dose given for the surgery, even if it was given on the previous day. Day 1 refers to the day following surgery. The average dose per injection will be determined as the average dose across all injections during the referenced time period. Total dose will be determined as the sum of all doses administered during the referenced time period.

Subjects will not be included in the surgery subgroup for a minor surgery. Data from minor surgeries from all subjects will be listed in the same format as used for major surgeries.

6.6. Study Drug Administration for PK Assessment

Study drug administered during clinic visits for the purpose of PK assessments will be listed. This includes the study drug administered, lot number, nominal IU amount administered per vial, actual IU amount administered per vial, number of vials injected, total actual IU injected, total volume injected, and infusion start and stop dates and times.

6.7. General Analysis Principles

Unless specified otherwise, only data occurring during the treatment period (efficacy period) will be used in analyses and summaries relating to bleeding, consumption, and compliance; efficacy data collected during the PK and surgical/rehabilitation periods (major and minor) will not be included (see Section 5.3.3).

6.7.1. Multiplicity

No adjustment for multiplicity will be made for the analyses of the different parameters.

7. PHARMACOKINETIC ANALYSES

7.1. Primary Endpoint

The primary endpoints include the following PK parameters derived from PK1 (rFVIIIFc manufactured at 2K scale) and from PK2 (rFVIIIFc manufactured at 15K scale) at the 15K baseline:

- AUC_{inf}
- Incremental recovery (IR)

as estimated from the FVIII activity data measured by aPTT clotting assay.

7.2. Secondary Endpoints

Secondary Pharmacokinetic endpoints are as follows:

PK parameters, including but not be limited to AUC_{inf}, IR, C_{max}, $t_{½}$, CL, V_{ss}, and MRT.
PK will be assessed using the one-stage (aPTT) clotting assay and the two-stage chromogenic assay for the following:

- 15K rFVIIIFc before treatment (at PK2) and after 13 weeks of treatment (at PK3)
- 15K rFVIIIFc at 1000 IU/vial and 6000 IU/vial strengths
- 2K rFVIIIFc (at PK1) and 15K rFVIIIFc (at PK2) [only C_{max}, $t_{½}$, CL, V_{ss}, and MRT; other parameters comprise the primary endpoint]

Pharmacokinetic (PK) analysis will be based on the Pharmacokinetic Analysis Set.

Non-compartmental analysis will be implemented in all subjects with sufficient data to estimate at least one PK parameter. Non-compartmental analysis will be performed on FVIII activity versus time data that were obtained following the IV infusion and adjusted for baseline and residual activity from prior therapy. If a repeat PK profile is required due to breakthrough bleeding (or any other reason) during the PK evaluations, then only the repeat profile will be used for the summary of FVIII activity levels and in the summary of PK parameters. For incomplete or nonevaluable PK profiles, only a subset of the PK parameters will be presented, as appropriate. Data from incomplete and nonevaluable rFVIIIFc PK profiles will not be used for the summary of FVIII activity levels but will be included in the SDTM datasets and FVIII activity listings.

Non-compartmental analysis will be conducted for FVIII activity data from both the one-stage activated partial thromboplastin time (aPTT) clotting and chromogenic assays using Phoenix WinNonlin software. Actual sampling times, doses, and infusion durations will be used for PK analyses. Nominal sampling times and doses will be used for the creation of tables, listings, and figures.

Descriptive statistics will be presented for all PK parameters identified in section 2.2.2 as measured by both the one-stage aPTT clotting and chromogenic assays following the rFVIIIFc injection for subjects included in the Pharmacokinetic Analysis Set. As such, only subjects who have complete and evaluable PK profiles will be included in the summary. For the purpose of presentation, the individual PK parameters are considered to be recorded to the number of

decimal places shown in Table 1. This will ensure 3 significant figures in the minimum value for each parameter. If necessary upon review of the final PK parameter estimates, the number of decimal places will be adjusted to ensure 3 significant figures in the minimum PK parameter value. This evaluation will be based on PK parameter estimates following the rFVIIIFc PK dose. Presentation of the data will follow the algorithm provided in Section 5.2.1.

Table 1: Number of decimal places for PK parameters

Parameter	Decimal places
Dose	1
IR	2
C_{max}	1
T_{max}	3
Lambda Z	4
Lambda (lower)	3
Lambda (upper)	1
$t_{1/2}$	2
CL	3
V_z	1
V_{ss}	1
MRT	2
AUC_{last}	0
AUC_{inf}	0
%AUC ext	3
DNAUC	1

The following analyses will be performed for the PK subgroup:

1. A summary table of FVIII activity levels will be provided for rFVIIIFc at scheduled PK timepoints by PK assessments (2K [PK1], 15K [PK2] and 15K [PK3]), by vial strength (15K [PK2]1000 IU/Vial , [PK3] 1000 IU/Vial and 15K [PK2] 6000 IU/Vial , [PK3] 6000 IU/Vial and by assay (one-stage [aPTT] clotting assay and two-stage chromogenic assay) for the Pharmacokinetic Analysis Set. A data listing of FVIII activity levels will be provided for rFVIIIFc; the listing will include actual dose administered and both the nominal and actual sampling times. All activity levels will be included in the data listing, whether or not the available samples were sufficient to determine all PK parameters.
2. PK parameters derived from non-compartmental analysis based on both the one-stage aPTT clotting and chromogenic assays for rFVIIIFc will be listed for each subject by PK assessments. The listing will contain all PK parameters that could be estimated by non-compartmental analysis and the subset of PK parameters from incomplete or nonevaluable PK profiles (eg, C_{max}, T_{max}, IR, and/or $t_{1/2}$).
3. PK parameters will be summarized descriptively by PK assessments and manufactured scale (2K [PK1], 15K [PK2] and 15K [PK3]), by vial strength (15K [PK2]1000 IU/Vial , [PK3] 1000 IU/Vial and 15K [PK2] 6000 IU/Vial , [PK3] 6000

IU/Vial and by assay (one-stage [aPTT] clotting assay and two-stage chromogenic assay) for the Pharmacokinetic Analysis Set.

4. FVIII activity versus time profiles for 2K [PK1], 15K [PK2] and 15K [PK3] will be plotted on the same graph for each subject in the Pharmacokinetic Analysis Set; only the activity curves for which all PK parameters could be determined will be included for the respective PK assessments. Mean activity versus time profiles will be constructed for rFVIIIFc for by PK assessments and manufactured scale (2K [PK1], 15K [PK2] and 15K [PK3]), by vial strength (15K [PK2]1000 IU/Vial , [PK3] 1000 IU/Vial and 15K [PK2] 6000 IU/Vial , [PK3] 6000 IU/Vial. Each set of plots will display the arithmetic mean ± SE. All graphs will be presented in both the linear and log scales and for one-stage [aPTT] clotting and two-stage chromogenic assays.

For the primary endpoint, the natural log transformed PK parameters (AUC_{inf} [if data permit], IR , C_{max}, $t_{½}$, CL, V_{ss}, and MRT) following rFVIIIFc dosing for 2K (PK1) and for 15K at the 15K baseline (PK2) measured by the one-stage [aPTT] assay) will be analyzed using a mixed effects model with scale and vials strength as fixed effect and subject as a random effect. Estimates of the adjusted mean differences (15K-2K) and corresponding 90% CIs will be obtained from the model. The adjusted mean differences and 90% CIs for the differences will be back transformed (exponentiated) to provide estimates of the ratio of adjusted geometric means (15K/2K) and 90% CIs for the ratios. Comparability of the 2 manufactured scales will be concluded if the 90% CIs for the ratio of adjusted geometric means for both primary PK endpoints (AUC_{inf} and IR following rFVIIIFc dosing for 2K and for 15K at the 15K baseline measured by the one-stage [aPTT] assay) fall within the range of (68%, 146%).

The same analysis will be performed on the remaining parameters [C_{max}, $t_{½}$, CL, V_{ss}, and MRT] measured by the one-stage [aPTT] assay and all PK parameters measured by the chromogenic assay following rFVIIIFc dosing for 2K (PK1) and 15K (PK2).

The comparability of vials of strength 1000 and 6000 IU for the primary endpoint PK parameters (AUCinf and IR only) following rFVIIIFc dosing 15K baseline (PK2) will be assessed. If these are not similar, further investigations will be carried out.

Since inclusion in the Pharmacokinetic Analysis Set requires a complete and evaluable PK profile from at least one of the two assays for any of the PK assessments, analyses for the aPTT clotting and chromogenic assays performed on the Pharmacokinetic Analysis Set will be based on different subjects if at least one subject has a complete and evaluable profile from only one of the assays.

FVIII activity levels for subjects during the peri-operative period will be listed separately.

7.3. Sensitivity PK Analysis

A sensitivity analysis will be performed on the primary endpoints only. The method for the analysis will be the same as above but the population will include only the subjects that have evaluable AUCinf and Incremental recovery (IR) for both PK1 and PK2 assessments.

8. EFFICACY ANALYSIS

8.1. General Efficacy Principles

No efficacy analysis is planned. However in the event of future requirement for analyses integrating data from this study with those from the extension study 8HA01EXT, efficacy endpoints will be defined in the SAP and will be derived in the analysis datasets, including prophylactic dose, dosing interval, consumption, total annualized 15K rFVIIIFc consumption, compliance, annualized bleeding rate, time from last injection of rFVIIIFc to the bleeding episodes, and the number of injections and dose of 15K rFVIIIFc to resolve a bleeding episode. Unless specified otherwise, only data occurring during the treatment period (efficacy period) will be used to derive endpoints relating to bleeding; efficacy data collected during the PK and surgical/rehabilitation periods (major and minor) will not be included (see Section 5.3.3). Endpoints and evaluations that are based on assessments at specified visits will utilize all data collected at those visits unless the visit was coincidental with a surgical/rehabilitation period for a major surgery, in which case it would be excluded.

8.1.1. Prophylactic Dose (IU/kg) and Dosing Interval (days)

The average weekly prophylactic dose (IU/kg) and the average prophylactic dosing interval will be based on prophylactic doses that are not separated by a bleeding episode or surgical/rehabilitation period (major or minor surgery). Data to be included in the calculations, specifically the prophylactic doses and the total duration of prophylaxis treatment, will come strictly from intervals representing 2 consecutive prophylactic doses (PR) during the treatment period (see Section 5.3.3 for a description of the treatment period). The sum of doses at PR_x and the sum of interval durations (PR_{x+1} minus PR_x) will be determined across all evaluable intervals of PR_x to PR_{x+1}. As such, when an event (a bleeding episode or surgery) is encountered the interval stops at the prophylactic dose prior to the event and continues with the first prophylactic dose after the event. The last PR dose in the study will be the end of the last interval used for these calculations.

$$\text{Average weekly prophylactic dose} = \frac{\text{Sum of doses at } PR_x}{\text{Sum of days in PR intervals}} \times 7$$

$$\text{Average prophylactic dosing interval} = \frac{\text{Sum of days in PR intervals}}{\text{Number of PR intervals}}$$

Prophylactic dosing will be further characterized by the number of prescribed changes in the dose and the number of prescribed changes in the dosing interval. Dose and dosing interval changes are based on recommendations made by the Investigator and may or may not reflect whatever modifications a subject actually made to his dosing regimen. The number of prescribed changes in the dose level and the number of prescribed changes in the dosing schedule will be summarized categorically (0, 1, 2, 3, 4, >4).

8.1.2. Consumption

The total annualized 15K rFVIIIFc consumption (IU/kg) will be calculated for each subject using the following formula:

$$\text{Annualized consumption} = \frac{\text{Total IU/kg of study drug received during the treatment period}}{\text{Total number of days during the treatment period}} \times 365.25$$

The total amount of 15K rFVIIIFc received will be the sum of the nominal IU/kg administered for each injection based on the units of 15K rFVIIIFc as recorded from the subject's diary and eCRF and his most recent weight.

Total annualized 15K rFVIIIFc consumption, including injections that were administered solely for the purpose of training, will be determined for the treatment period (i.e., excluding the PK period and surgery/rehabilitation periods [major and minor surgeries]). Consumption during surgery/rehabilitation periods will be listed separately.

8.1.3. Compliance

Prophylactic dose compliance will assess adherence to the Investigator's recommendations for dosing. Prophylactic dose compliance will be assessed during the treatment period.

Except for doses administered in the clinic, study treatment may be administered by a caregiver or self-administered by the older children in the study.

Data from the eCRF and EPD will be considered for the analysis of treatment received and subjects' compliance with the study protocol; compliance has been defined by the Sponsor.

8.1.3.1. Compliance of Prophylactic Injections

The compliance rate of each subject to the prescribed prophylactic dosing regimen during the treatment period will be calculated in 2 ways, as dose compliance and as dosing interval compliance. Compliance will first be determined on a per-injection basis and then on a per-subject basis. That is, compliance for an individual dose or dosing interval will be determined and then the overall percentage of doses and dosing intervals that were in compliance will be determined for each subject.

For the purpose of evaluating compliance, the following will be considered per injection:

- the nominal dose taken compared to the nominal dose prescribed
- the actual day of treatment compared to the prescribed day of treatment

An individual dose will be considered compliant if it is within 80% to 125% of the prescribed dose. An individual dosing interval will be considered compliant if the time between two prophylactic doses is within 24 hours of the prescribed dosing interval. Prescribed dose and dosing intervals are according to the Investigator. Instructions provided to the subject by the Investigator regarding dose or dosing interval changes will be used to determine compliance as of the date the information was provided to the subject.

The actual dosing intervals will be calculated as the length of time between consecutive prophylactics doses (date/time of PR_{x+1} – date/time of PR_x). PR_{x+1} and PR_x are also discussed in Section 8.1.1. The actual time between doses will be determined in minutes and converted to days as the number of minutes divided by 1440. The prescribed dosing interval will be taken

from the eCRF as recorded by the Investigator. The absolute value of the difference between the actual and prescribed dosing intervals must be ≤1 day (+/- 24 hours) in order to be compliant.

All prophylactic injections will be used to determine prophylactic dose compliance; only the prophylactic injections used to determine the average prophylactic dosing interval (i.e., intervals not separated by a bleeding episode or surgical/rehabilitation period), as detailed in Section 8.1.1 will be used to evaluate prophylactic interval compliance. Dose and dosing interval compliance rates per subject will be determined as follows:

$$\text{Dose compliance rate} = \frac{\text{Number of doses taken within 80\% to 125\% of prescribed dose}}{\text{Total number of doses}} \times 100$$

Where the percentage of a prescribed dose is calculated as: (nominal dose taken/prescribed dose) x100

and the 'nominal dose taken' will be determined from the nominal potency labeled on the vials used by the subject for each injection of 15K rFVIIIFc.

$$\text{Dose interval compliance rate} = \frac{\text{Number of doses taken within +/- 24 hours of prescribed day/time}}{\text{Total number of intervals}} \times 100$$

8.1.4. Compliance of EPD data entry.

The Overall percentage of injections entered into ePD within 7 days of administration will be calculated for each subject and the following subgroup will be calculated:

- less than 80% and
- greater or equal than 80%

of their total individual ePD records entered within this 7 day window.

8.1.5. Total Annualized rFVIIIFc Consumption

The total annualized 15K rFVIIIFc consumption per subject for the prevention and treatment of bleeding episodes will be listed. See Section 8.1.2 for details on the annualized 15K rFVIIIFc consumption derivation. The listing will also be provided for:

- prophylactic injections
- injections administered for a bleeding episode, including for follow-up
- all other injections

8.1.6. Bleeding Episodes

Bleeding episodes will be recorded in the both the EPD and eCRF; during the course of the study the investigator was given the opportunity to disagree with the type of bleed (spontaneous, traumatic, other) as classified by the subject and the subject was subsequently given the opportunity to agree or disagree with the reclassification. If the subject agreed with the

Investigator's assessment, then all analyses subset by type of bleed will be based on the Investigator's determination of the bleed type whether or not the change was made to the subject's records.

A standardized definition of a bleeding episode has been applied to this study, as follows: A bleeding episode starts from the first sign of a bleed, and ends no more than 72 hours after the last treatment for the bleed, within which any symptoms of bleeding at the same location, or injections less than or equal to 72 hours apart, are considered the same bleed. Any injection to treat the bleed taken more than 72 hours after the preceding one will be considered the first injection to treat a new bleed. For the purpose of analysis, the latter injection will be associated with a new bleeding episode and classified as type=Unknown. The location(s) associated with the original bleeding episode will be carried forth to the new bleeding episode; the onset date and time of bleeding will be unknown and hence considered missing. Any bleeding at a different location is considered a separate bleeding episode regardless of the time from the last injection.

This algorithm will also apply when a follow-up injection was recorded subsequent to a prophylactic injection. If the follow-up injection was administered >72 hours after the previous injection to treat a bleeding episode (type=spontaneous, traumatic, follow-up), then the follow-up injection will be classified as a new bleeding episode as described above.

Bleeding at a different location will occur when the general bleeding location is different (e.g., in a joint for the original bleeding episode and subsequently in a muscle) or in a sub-location not initially present if in the same location category (e.g., right elbow for the original bleeding episode and subsequently in the right and left elbows). Conversely, a bleeding episode that originally occurs in the right elbow and left knee and is reported as a new bleed within 72 hours as being only in the right elbow will be considered to be in the same location and hence not counted as a new bleeding episode.

A bleeding episode that occurs in multiple locations will be counted as a single event when determining the overall annualized number of bleeding episodes. However, in summaries by bleeding location, the bleeding episode will be counted in each location for which it is reported with the exception that bleeding that occurs in more than one sub-location of the same location category (e.g., 2 or more different joints) will be counted just one for that location category.

Only bleeding episodes that were treated with at least one dose of FVIII (whether rFVIIIFc or a non-study drug) will be included evaluating bleeding. That is, bleeding episodes that were not treated at all will not be included. Bleeding episodes that were treated with non-study medication will be included in the determination of the annualized bleeding rate. The handling of bleeding episodes treated with non-study FVIII for other endpoints is discussed in sections 8.1.8 , 8.1.9.1 and 8.1.9.2.

Bleeding episodes of an unknown type will be included in the determination of the annualized bleeding rate and in summaries based on bleeding episodes.

The per-subject annualized number of bleeding episodes, hereafter referred to as the annualized bleeding rate (ABR), will be calculated for each subject using the following formula:

$$\text{ABR} = \frac{\text{Number of bleeding episodes during the treatment period}}{\text{Total number of days during the treatment period}} \times 365.25$$

8.1.7. Annualized Bleeding Rate

The per-subject ABR will be listed. All types of bleeding episodes (spontaneous, traumatic, and type unknown) will be included in determining the annualized number. As a description of the raw data collected in this study, the unadjusted number of bleeding episodes per subject will be listed using categorical (0, 1, 2, 3, 4, 5, and >5).

8.1.8. Time from Last Injection of rFVIIIFc to a Bleeding Episode

The duration of time between a spontaneous bleeding episode and the most recent previous prophylaxis injection of 15K rFVIIIFc, will be calculated and listed per each subject. Time will be determined in minutes and then converted to days as total minutes divided by 1440. Of note, the reference time for the bleeding episode is the onset of the bleed and not the time treatment for the bleed was first administered. The definition of a new bleeding episode can be found in Section 7.1.1

The time from the last prophylactic injection to a new spontaneous bleeding episode will be determined on both a per-bleeding episode and per-subject basis. Each evaluable spontaneous bleeding episode will be included as a separate observation in the summary statistics for the per-bleeding episode evaluation. Evaluable bleeding episodes are those for which both a date and time are available for both the onset of the bleeding episode and the previous prophylactic injection. For the per-subject evaluations, times will be averaged across all evaluable spontaneous bleeding episodes per subject and descriptive statistics will be provided for this per-subject average time.

Bleeding episodes that were treated with non-study medication will be included in these analyses, regardless of which treatment was administered first, if all other information needed to calculate the endpoint value is available.

8.1.9. Resolution of a Bleeding Episode

8.1.9.1. Number of Injections and Dose of rFVIIIFc to Resolve a Bleeding Episode

The number of injections and average dose per injection (IU/kg) required to resolve a bleeding episode will be determined on both a per-bleeding episode and per-subject basis. For completeness, the total dose (IU/kg) administered to resolve a bleeding episode will also be determined on both a per-bleeding episode and per-subject basis. See Section 7.1.1 for details on the definition of a bleeding episode. A bleeding episode is considered resolved when treatment for the bleeding is no longer needed.

Per bleeding episode: The total number of injections will include the initial injection for a spontaneous bleed (SB), a traumatic bleed (TB), or a bleed of unknown type plus all injections identified as follow-up (FU) treatment for that bleed. For each bleed, the average dose per injection will be calculated as the average of all doses (IU/kg) administered among the SB/TB/Unknown and FU injections administered to treat that bleed; the total dose will be the sum of these doses. The average dose per injection and total dose required for resolution of a bleeding episode will be calculated.

Per subject: The number of injections, average dose per injection, and total dose required to resolve each bleeding episode, as determined for the per-bleeding episode summaries, will be averaged across all bleeding episodes for each subject. Bleeding episodes that were treated with non-study medication will be included in the determination of the number of injections required

to resolve the bleeding episode but not in either the average dose per injection or total dose required.

8.1.9.2. Time Between the First and Second Injection to Treat a Bleeding Episode

In order to characterize the resolution of bleeding episodes treated with 15K rFVIIIFc, the time between the first and second injections to treat a bleeding episode will be determined on both a per-bleeding episode and a per-subject basis.

The time (in hours) between the first and second injections to treat a bleed will listed for each bleeding episode, including those with type=Unknown, that required at least 2 injections for resolution.

The number of hours between the first and second injections to treat a bleeding episode for each subject will be calculated.

Additionally, the time between the first and second injections to treat a bleed will be listed overall by type of bleed (spontaneous, traumatic).

Bleeding episodes that were treated with non-study medication will be included in the determination of the time between the first and second injections.

9. SAFETY ANALYSIS

In general, Safety data, including AE data, laboratory data, and data on inhibitor and FVIII antibody, will be listed by manufactured scale (2K and 15K see section 5.1) and summarized for the Safety Analysis Set.

9.1. Primary Safety Endpoint

There are no primary safety endpoints in this study.

9.2. Secondary Safety Endpoints

9.2.1. Adverse Events

An AE is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product that does not necessarily have a causal relationship with this treatment. AEs will be classified using the Medical Dictionary for Regulatory Activities (MedDRA) system organ classes and preferred terms. The most up to date MedDRA version will be used throughout the study. All AEs, including serious pre-treatment AEs (if recorded), will be listed.

The AEs that occur during the time the subject is treated rFVIIIFc 2K scale drug product (between first rFVIIIFc 2K [PK1] dose up to the first rFVIIIFc 15K [PK2] dose) will be flagged (see section 5.1).

AEs that occurred during major surgical/rehabilitation periods will be included in the overall (top-line) summary of AEs but not in any of the other AE tables. All adverse event listings will include the onset and resolution study days relative to rFVIIIFc (2K or 15K), as described in Section 5.1. AEs that are emergent during a major surgical/rehabilitation period, and AEs that are emergent on the day of surgery will be flagged.

AEs occurring during a major surgical/rehabilitation period with an onset date on the day the surgical/rehabilitation period starts or on the day of the surgery will be included in the summaries of the overall study AEs. Consideration is given to adverse events with an onset date at the start of the surgical/rehabilitation period in the event the pre-surgical dose was administered the day before the surgery.

Events of overdose will not be included in the AE summary tables unless they are determined to be adverse events.

9.2.2. Overall (Top-line) Summary of Treatment-emergent Adverse Events

A top-line summary of treatment-emergent adverse events (TEAEs) will be provided which tabulates the number and percentage of subjects who experienced a TEAE, related TEAE, treatment-emergent SAE, or treatment-emergent related SAE; the number and percentage of subjects who discontinued treatment and/or the study due to a TEAE; and the number and percentage of subjects who died. The total number of subject-years of follow-up and the total number of exposure days will also be provided in this top-line summary. The total number of subject years of follow-up will include the time between the Week 26/End-of-Study visit and the follow-up phone call for subjects who do not rollover into the extension study. Subject-years of follow-up and exposure days during major surgical/rehabilitation periods will not be included within the vial strengths but will be included in the total column. TEAEs occurring after the start

of the first rFVIIIFc 2K [PK1] dose up to the second rFVIIIFc 15K [PK2] dose will be considered separately from the treatment period of rFVIIIFc treatment (between PK2 and to the last study visit) . TEAEs will be summarized by manufactured scales 2K and 15K and overall.

9.2.3. Treatment-emergent Adverse Events

An AE will be regarded as treatment-emergent if it was present prior to receiving the first injection of rFVIIIFc and subsequently worsened in severity, or was not present prior to receiving the first injection but subsequently appeared before the subject's last visit on study or the follow-up phone call, whichever came later (or the date of withdrawal/loss to follow-up).

TEAEs occurring between the first rFVIIIFc 2K [PK1] dose up to first rFVIIIFc 15K [PK2] dose will be considered separatelyso that TEAEs can be summarized by manufactured scales 2K and 15K. .

The algorithm for the determination of treatment emergence when an onset date is partially or completely missing is described below.

- If the onset time of an adverse event (if time is collected) is missing and the date of onset is the date of dosing, the AE is considered to be a TEAE.
- If the onset day of an adverse event is missing and the month and year of the onset of the AE are either the same or later than the month and year of the first treatment, the AE will be considered a TEAE.
- If the onset day of an adverse event is missing and the month and year of the onset of the AE precede the month and year of the first treatment, the AE will not be considered a TEAE.
- If the onset month of an adverse event is missing and the year of the onset of the AE is either the same as or later than the year of first treatment, then the AE will be considered a TEAE.
- If the onset month of an adverse event is missing and the year of AE onset proceeds the year of first treatment, the AE will not be considered a TEAE.
- If the onset day, month, and year of an adverse event are missing, the AE will be considered to be a TEAE.
- If start date is partial but the stop date can be determined to be before the start of the first dose of study drug, then the AE will not be considered a TEAE.

The overall incidence of adverse events treatment emergent to 2K and 15K rFVIIIFc will be summarized by system organ class (SOC) and preferred term separatly. Unless specified otherwise, SOCs and preferred terms within each SOC will be presented alphabetically. For the purpose of summarization, a subject is counted once in a SOC or preferred term if the subject reported one or more events in that SOC or preferred term. Percentages will be based on the overall number of subjects.

9.2.4. Adverse Events in Descending Order of Incidence

A table will be provided which displays AE preferred terms in descending order of incidence on the overall incidences. Only preferred terms will be included in this table (i.e., the display will not include SOCs).

A similar table will be provided for just severe AEs. AEs for which the assessment of severity is missing will be included in this table.

These tables will also be presented by subgroup based upon contemporaneous entry compliance (<80% and ≥80) as described in Section 10.

9.2.5. Severity of Adverse Events

An overall summary of TEAEs, occurred during 15K treatment, by system organ class, preferred term, and severity (mild, moderate, severe) will be presented. AEs with a missing severity will be counted as "severe" in the summary table. A subject will be counted once for each SOC and preferred term based on the greatest severity within that SOC and preferred term, respectively.

This table will also be presented by subgroup based upon contemporaneous entry compliance (<80% and ≥80%) as described in Section 10.

9.2.6. Relationship of Adverse Events to Study Drug

AEs are classified by the Investigator for relationship to study drug ("Not related" and "Related"). An overall summary of TEAEs, occurred during 15K treatment, by SOC, preferred term, and relationship will be presented. AEs with a missing relationship will be counted as "Related" in the summary table. A subject will be counted once for each SOC and preferred term based on the highest relationship within that SOC and preferred term, respectively.

This table will also be presented by subgroup based upon contemporaneous entry compliance (<80% and ≥80%) as described in Section 10.

9.2.7. Serious Adverse Events

Any AE reported as resulting in death, immediate risk of death (life threatening), inpatient hospitalization or prolongation of existing hospitalization, persistent or significant disability/incapacity, or a congenital/anomaly/birth defect will be classified as an SAE. An SAE may also be any other medically important event that, in the opinion of the Investigator, may jeopardize the subject or may require intervention to prevent one of the other outcomes listed above. Events considered medically important, as defined in Section 15.2.3 of the protocol, are also considered to be SAEs.

All SAEs will be listed; overall treatment-emergent SAEs, occurred during 15K treatment, will be summarized by system organ class and preferred term.

This table will also be presented by subgroup based upon contemporaneous entry compliance (<80% and ≥80%) as described in Section 10.

9.2.8. Adverse Events Leading to Treatment Discontinuation or Withdrawal From the Study

AEs leading to treatment discontinuation or withdrawal from the study will be listed. All AEs reported on the AE log with "Was the subject terminated from this study due to this AE" as "Yes" or "Action Taken with Study Drug" with a response of "Drug Withdrawn" will be included.

9.2.9. Deaths on Study

A listing of deaths occurring on the study will be provided.

9.3. Clinical Laboratory Evaluations

Using the dates and times of the first dose of rFVIIIFc and blood draws for laboratory evaluations; baseline is defined as the last non-missing evaluable assessment taken prior and closest to the first dose of rFVIIIFc, presumably screening value. Post-baseline laboratory results are defined as any assessment taken after the start of the first dose of rFVIIIFc. In the case of retests being taken for the same visit number assigned, the latest available non-missing assessment for that visit will be used for by-visit summaries. All the overall laboratory evaluations will be summarized for the Safety Analysis Set.

All summaries will be structured such that the laboratory tests are presented in the order shown in the tables provided in Section 9.3.4.

All laboratory data will be provided in data listings. Laboratory evaluations taken during major surgical/rehabilitation periods will be included in the listings and flagged. In addition, subjects with an abnormal laboratory result based on the lower and upper limits of the normal range will be listed separately. Similarly, subjects with an abnormal laboratory result based on the potentially clinically significant abnormal levels will be listed separately. All hematology and chemistry laboratory results will be provided for these subjects; abnormal values will be identified.

9.3.1. Hematology and Chemistry

Hematology measurements that will be collected and summarized include: white blood cell count (WBC) and differential, red blood cell count (RBC), hemoglobin, hematocrit, and platelet count.

Chemistry measurements that will be collected and summarized include: sodium, potassium, chloride, glucose, total protein, total bilirubin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), blood urea nitrogen (BUN), serum creatinine, and gamma glutamyl transferase (GGT).

9.3.2. Change from Baseline

Hematology and chemistry results at baseline and post baseline visits, along with change from baseline, will be summarized with descriptive statistics by visit and for the end of study (based on last observation carried forward). Data from unscheduled visits will be excluded from this analysis.

9.3.3. Shifts

Each subject's laboratory values will be classified according to whether the test result is "low" (below the lower limit of normal [LLN]), "normal" (within the normal range), "high" (above the upper limit of normal [ULN]). Shift tables will be constructed based on both the minimum and maximum post baseline values for each subject. Data collected from unscheduled visits will be included in the determination of the per subject minimum and maximum values. A separate table will be provided which summarizes the results of the shift tables in which the number and percentage of subjects with a shift to low (from normal, high, or unknown) and the number of subjects with a shift to high (from normal, low, or unknown) will be tabulated; percentages will be based on the number of subjects at risk. The number at risk for a shift to low (high) is the number of subjects whose baseline value was not low (high), including unknown, who had at least one post-baseline value. Only directions of change indicating a clinical concern will be included in this table summarizing the shifts. The direction of concern is provided in Table 2.

Table 2: Direction of Change Indicating Clinical Concern for Laboratory Tests

Laboratory Test	Direction	Laboratory Test	Direction
Chemistry		Hematology	
Liver		White blood cells	Low and High
ALT/SGPT	High	Lymphocytes	Low and High
AST/SGOT	High	Neutrophils	Low and High
Total bilirubin	High	Monocytes	Low and High
GGT	High	Eosinophils	Low and High
Renal		Basophils	Low and High
Blood urea nitrogen	High	Red blood cells	Low and High
Creatinine	High	Hemoglobin	Low and High
Electrolytes		Hematocrit	Low and High
Sodium	Low and High	Platelets	Low and High
Potassium	Low and High		
Chloride	Low and High		
Other			
Glucose	Low and High		
Total protein	Low and High		

9.3.4. Potentially Clinically Significant Laboratory Abnormalities

Abnormal laboratory values will also be evaluated by determining the number and percentage of subjects with at least one potentially clinically significant laboratory abnormality over the course of the study that also represents a worsening from baseline. The potentially clinically significant levels are based on Grade 2 or higher thresholds from the Common Toxicity Criteria for Adverse Events (CTCAE v 4.02 2009) where possible, or were defined by Biogen's Safety and Benefit Risk Management group. Subjects who have a post baseline laboratory value that meets the

criteria for being potentially clinically significant but do not have a baseline value will be included in the numerator for determining the percentage of subjects with an abnormality. Percentages will be based on the number of subjects with at least one post baseline value for the given laboratory test. Threshold levels for potentially clinically significant laboratory abnormalities are provided in Table 3 (hematology) and Table 4 (chemistry). Data collected from unscheduled visits will be included in this analysis.

Table 3: Threshold Levels for Potentially Clinically Significant Hematology Abnormalities

	Low	High
Neutrophils	<1.5 x 10^9/L	NA
Eosinophils	NA	>1.6 × 10^9/L
Hemoglobin	<100 g/L	Increase in >20 g/L above ULN
Hematocrit	<30%	≥60%
Platelet count	≤75 x 10^9/L	≥700 × 10^9/L

NA = not applicable

Table 4: Threshold Levels for Potentially Clinically Significant Chemistry Abnormalities

	Low	High
Liver		
ALT/SGPT	NA	>3 × ULN
AST/SGOT	NA	>3 × ULN
Total bilirubin	NA	>1.5 × ULN
GGT	NA	>2.5 × ULN
Renal		
Creatinine	NA	>1.5 × ULN
Electrolytes		
Chloride	≤90 mmol/L	≥118 mmol/L
Other		
Glucose	<3.1 mmol/L	>8.9 mmol/L
Total protein	≤45 g/L	≥100 g/L

NA = not applicable, ULN = upper limit of normal

9.3.5. Incidence of Inhibitor Development

All inhibitor results of the Nijmegen-modified Bethesda Assay from the central lab will be listed. Results from blood samples collected during surgical/rehabilitation periods for the purpose of determining the presence of an inhibitor will be included in the listing.

Inhibitor results of the Nijmegen-modified Bethesda Assay from the central lab will be summarized for the Safety Analysis Set. Results from blood samples collected during surgical/rehabilitation periods for the purpose of determining the presence of an inhibitor will be included in this analysis.

A positive inhibitor occurs where a subject has a value ≥0.6 Bethesda Units (BU/mL) confirmed on re-testing within 2 to 4 weeks. Both tests must be performed by the central laboratory.

A "low" titer inhibitor occurs where a subject has a value ≥0.6 but <5.0 Bethesda Units (BU/mL) confirmed on re-testing within 2 to 4 weeks.

A "high" titer inhibitor occurs where a subject has a value ≥5.0 Bethesda Units (BU/mL) confirmed on re-testing within 2 to 4 weeks.

Incidences for all subjects will be summarized for any positive, low, and high titers. The numerator for all analyses will include the number of subjects who tested positive for an inhibitor.

- To calculate the proportion of subjects with a confirmed inhibitor for all subjects, subjects who develop a confirmed inhibitor during the course of the study following the initial rFVIIIFc administration will be counted in the numerator; all subjects in the Safety Analysis Set with at least 1 valid inhibitor test after receiving rFVIIIFc will be counted in the denominator.

An exact 95% confidence interval for the proportion of subjects with a confirmed inhibitor will be calculated using the Clopper-Pearson method for a binomial proportion. SAS version 9.4 or higher will be used to produce the exact confidence interval, with PROC FREQ producing Clopper-Pearson confidence intervals as the default method.

9.3.6. Incidence of Anti-rFVIIIFc Antibodies

The development of anti-rFVIIIFc antibodies will be assessed as the number and percentage of subjects negative throughout the study, at each study visit, at any time following treatment with rFVIIIFc, and at the final evaluation. Percentages will be based on the number of subjects who are antibody negative prior to treatment with rFVIIIFc and have at a post baseline antibody evaluation for the referenced time point or time interval.

Results from blood samples collected during surgical/rehabilitation periods for the purpose of determining the presence of anti-rFVIIIFc antibodies will be included in this analysis.

In addition to a listing of all anti-rFVIIIFc antibody results, a separate listing of all results from subjects with at least one positive outcome during the study, including at baseline, will be provided.

9.3.7. Vital Signs

Vital signs (systolic and diastolic blood pressure, pulse, respiratory rate, and oral temperature) will be listed only; summary tables are not planned.

10. ADDITIONAL SUBGROUP ANALYSES

A subgroup analyses of compliance of EPD data entry (<80% and ≥80%), will be performed only if at least 5 subjects are in both subgroups.
The percentage will be summarized with descriptive statistics and categorically (<80% and ≥80%); Duration of dosing and adverse event tables will be repeated using the subgroup categories see sections 6.5.1.2 and 9.2 for details.
This flag will also be included in all listings of study drug injection and adverse event data.

11. INTERIM ANALYSES

An interim database lock is planned once all subjects enrolled have had the first PK assessment (PK1). No interim analysis is planned for the purposes of this study; however, the evaluable data from PK1 will be used together with samples from studies 997HA307 and 8HA02PED to evaluate the predictive accuracy of Hemophilia Pharmacokinetic Tool (HPT).
Analyses to be performed are detailed in a separate HPT analysis statistical analysis plan, and will be documented in a separate report.

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13. INDEPENDENT DATA SAFETY MONITORING COMMITTEE

There will be no independent data safety monitoring committee for this study.

14. CHANGES TO PLANNED ANALYSES

14.1. Changes from Version 1.1 of the Protocol

The following changes have been made to the statistical approach specified in version 1.1 of the protocol:

The PK analysis will be performed using the Pharmacokinetic Analysis Set (defined in Section 4.4) instead of the Sequential Pharmacokinetic Subgroup population (which was defined in the protocol as all subjects who have evaluable PK profiles for PK2 and for at least 1 of PK1 and PK3).

The PKAS and the specified mixed model allow use of all PK data available. For the primary endpoint, an extra sensitivity analysis will be carried out on the subjects that have evaluable PK for PK1 and PK2 parameters.

For more clarity the fixed effect model has been re-labelled and scale and vials strengths have been used in the description instead of period and treatment.

An extra subgroup analysis has been defined for some safety endpoints this analysis for will be performed only if at least 5 subjects are in both subgroups.

LIST OF TABLES, LISTINGS, AND FIGURES

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Summary of 15K rFVIIIFc treatment-emergent adverse events by severity by ePD entry compliance
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Mean (+/- SE) FVIIII Activity over Time by vial strength 1000 IU/Vial , 6000 IU/Vial) and PK2 and PK3 assessments:Two-stage chromogenic assay (Log scale)