	Statistical Analysis Plan	**Final v1.0**

998HB303

STATISTICAL ANALYSIS PLAN

Bioverativ	Statistical Analysis Plan	Final v1.0

STATISTICAL ANALYSIS PLAN

Product Studied: Recombinant Factor IX Fc Fusion Protein (rFIXFc)

Protocol Number(s): 998HB303

An Open-Label, Multicenter Evaluation of the Safety and Efficacy of Recombinant Coagulation Factor IX Fc Fusion Protein (rFIXFc; BIIB029) in the Prevention and Treatment of Bleeding in Previously Untreated Patients With Severe Hemophilia B

Date of Protocol: 06 August 2018 (Version 3)

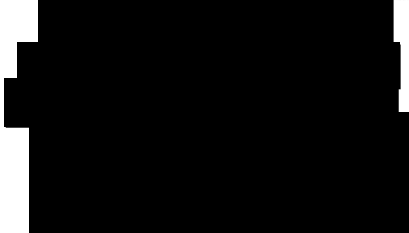**Date of Statistical Analysis Plan:** 26 February, 2019

Approved By:

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TABLE OF CONTENTS

LIST OF ABBREVIATIONS

ABR	Annualized Bleeding Rate
AE	Adverse Event
ALT/SGPT	Alanine Aminotransferase
AST/SGOT	Aspartate Aminotransferase
BU	Bethesda Units
BUN	Blood Urea Nitrogen
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
C_{max}	Maximum Plasma Activity/Concentration
CRO	Contract Research Organization
CS	Clinically Significant
CSR	Clinical Study Report
CTCAE	Common Toxicity Criteria for Adverse Events
dL	Deciliter
DSMC	Data Safety Monitoring Committee
eCRF	Electronic Case Report Form
ED	Exposure Day
EMA	European Medicines Agency
EOS	End of Study
EOT	End of Treatment
EPD	Electronic Patient Diary
ET	Early Termination
FAS	Full Analysis Set
FIX	Coagulation Factor IX
FU	Follow-up
GGT	Gamma Glutamyl Transferase
IR	Incremental Recovery
ITI	Immune Tolerance Induction
IU	International Unit

IXRS	Interactive Voice/Web Response System
L	Litre
LLN	Lower Limit of Normal
LLOQ	Lower Limit of Quantification
MedDRA	Medical Dictionary for Regulatory Activities
MHRA	Medicines and Healthcare products Regulatory Agency
mL	Millilitre
mmol	Millimole
NCS	Not Clinically Significant
PD	Plasma Derived
PK	Pharmacokinetic
PRO	Patient Reported Outcome
PT	Preferred Term
PTP	Previously Treated Patient
PUP	Previously Untreated Patient
RBC	Red Blood Cell Count
rFIXFc	Recombinant Coagulation Factor IX Fc Fusion Protein
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SB	Spontaneous Bleed
SD	Standard Deviation
SOC	System Organ Class
SVC	Single Vial Consolidation
TEAE	Treatment Emergent Adverse Event
TB	Traumatic Bleed
ULN	Upper Limit of Normal
ULOQ	Upper Limit of Quantification
WBC	White Blood Cell Count
WHO	World Health Organization

1. INTRODUCTION

Study 998HB303 is a Phase 3, open label, single arm, multicenter study designed to evaluate the safety and efficacy of recombinant coagulation factor IX Fc fusion protein (rFIXFc; BIIB029) in the prevention and treatment of bleeding in previously untreated male patients < 18 years of age with severe hemophilia B, in accordance with the EMA CHMP guideline on clinical investigation of recombinant and human plasma-derived factor IX products.[1]

This statistical analysis plan (SAP) will describe the final analysis of 998HB303 study data when at least 20 patients have reached at least 50 EDs with rFIXFc.

This SAP is based on Version 3 of the approved study protocol dated 06 August 2018 and more complete details of the study can be found therein.

2. STUDY OBJECTIVES AND ENDPOINTS

2.1. Study Objectives

2.1.1. Primary Objective

The primary objective of the study is to evaluate the safety of rFIXFc in previously untreated patients (PUPs) with severe hemophilia B.

2.1.2. Secondary Objectives

The secondary objectives of this study are:

- To evaluate the efficacy of rFIXFc in the prevention and treatment of bleeding episodes in PUPs.

- To evaluate rFIXFc consumption for the prevention and treatment of bleeding episodes in PUPs.

2.1.3. Exploratory Objectives

The exploratory objective of this study is to evaluate the effect of rFIXFc based on patient-reported outcomes (PROs) and health resource utilization.

2.2. Study Endpoints

2.2.1. Primary Endpoint

The primary endpoint of this study is the occurrence of inhibitor development.

2.2.2. Secondary Endpoints

The secondary endpoints of the study are as follows:

- The annualized number of bleeding episodes per patient (annualized bleeding rate [ABR]).

- The annualized number of spontaneous joint bleeding episodes per patient.

- Assessments of response to treatment with rFIXFc for bleeding episodes, using the 4-point bleeding response scale (Investigator assessment for bleeding episodes treated in the clinic; parent or caregiver assessment for all other bleeding episodes).

- Total number of EDs per patient per year.

- Total annualized rFIXFc consumption per patient for the prevention and treatment of bleeding episodes.

- The number of injections and dose per injection of rFIXFc required to resolve a bleeding episode.

- rFIXFc incremental recovery (IR).

2.2.3. Exploratory Endpoints

The exploratory endpoints include, but are not limited to:

- Health outcomes.

2.2.4. Pharmacokinetic Endpoints

The only pharmacokinetic (PK) endpoint in this study is rFIXFc IR, as specified in Section 2.2.2.

2.2.5. Pharmacodynamic Endpoints

There is no pharmacodynamic endpoint in this study.

3. STUDY DESIGN

3.1. Overall Study Design and Plan

This study is open label, single arm, and multicenter, designed to evaluate the safety and efficacy of rFIXFc in PUPs with severe hemophilia B when used according to local standard of care for implementation of a prophylactic regimen, including an optional preceding episodic (on-demand) treatment regimen.

The study period consists of screening, treatment, and follow-up. Individual patient study participation is expected to be approximately 6 months to 3 years including screening and follow-up. The treatment period comprises 3 possible regimens: An optional episodic regimen; a prophylactic regimen required for all patients; and an immune tolerance induction (ITI) regimen only for patients who develop inhibitors.

Approximately 30 patients will be enrolled to achieve at least 20 patients with no less than 50 EDs by the end of the study. One ED is defined as a 24-hour period in which a patient receives one or more doses of rFIXFc, with the time of the first injection of rFIXFc defined as the start of the ED.

3.1.1. Study Sample

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

3.1.2. Treatment Arms

This is a single-arm study. All patients will be treated with study drug rFIXFc.

Within this single arm, there are 3 possible treatment regimens: An optional episodic (on-demand) regimen; a required prophylactic regimen for all patients; and an ITI regimen available only for patients who develop an inhibitor as defined in Section 3.1.2.3.

3.1.2.1. Episodic Treatment Regimen

Once eligibility has been confirmed and the subject has been enrolled, the Investigator has the option to treat the subject episodically, until a prophylactic regimen is initiated. Dosing will be determined by the Investigator using the guidelines in Appendix A of the approved protocol. The duration of episodic treatment is at the Investigator's discretion. Date of transition from episodic treatment to prophylactic treatment is captured on the study electronic case report form (eCRF).

3.1.2.2. Prophylactic Treatment Regimen

The use of a prophylactic treatment regimen in young children is currently the recommended standard of care in hemophilia due to the demonstrated benefit on long-term outcomes. It is anticipated that patients will begin a prophylactic treatment regimen prior to or immediately following the occurrence of a third hemarthrosis (joint bleed). The recommended initial prophylactic regimen is 50 IU/kg weekly. Adjustments to the dose and dosing interval can be made based upon available incremental recovery data, subsequent FIX activity levels, level of

physical activity, and bleeding pattern, in accordance with local standards of care for a prophylactic regimen.

Prophylactic treatment will continue until the patient reaches at least 50 EDs to study drug, discontinues, begins an ITI regimen, or the end of study is declared by Bioverativ.

3.1.2.3.   Immune Tolerance Induction (ITI) Treatment Regimen

Immune tolerance induction (ITI) with rFIXFc is allowed during the study for those subjects developing a positive high-titer inhibitor or a positive low-titer inhibitor (both defined in Section 5.2.4) with poorly controlled bleeding. The Medical Monitor will work with the Investigator to ascertain an established ITI regimen of the Investigator's choice. The ITI regimen plan must be approved for each subject by Bioverativ's Study Medical Director. A separate consent is required before starting the ITI regimen.

Duration of ITI treatment is up to 24 months, or until the criteria for successful immune tolerance are met. The criteria for successful immune tolerance are described in Section 10.2.6.5 of the protocol. Patients who choose to discontinue ITI prior to meeting the criteria for success will be withdrawn from the study.

3.1.3.   End of Study

End of the study (EOS) will occur when at least 20 patients have reached at least 50 EDs with rFIXFc and had at least one inhibitor test performed at or beyond 50 EDs.

3.1.4.   Independent Data Monitoring Committee

An independent, external Data Safety Monitoring Committee (DSMC) is responsible for evaluating and monitoring the safety and tolerability of the study drug on an ongoing basis during the study. The specifics regarding the DSMC organization and procedures are outlined in the DSMC Charter.

3.2.   Statistical Hypothesis

There is no statistical hypothesis for this study as all but the primary endpoint will be analyzed descriptively only. The methodology for analysis of the primary endpoint is described in Section 9.4.3.

3.3.   Sample Size Justification

The planned total sample size for this study is approximately 30 patients.

Because the size of the hemophilia population is limited, the sample size is based on clinical rather than statistical considerations. Taking into account the CHMP Guideline[1] and in an effort to enroll a sufficient number of patients to assess the efficacy and safety of rFIXFc in this population of primarily very young children, approximately 30 patients will be enrolled to achieve at least 20 patients with no less than 50 EDs by the completion of the study.

3.4.   Randomization and Blinding

This is an open-label single arm study so there is no blinding or randomization.

3.5.   Interim Analysis

No interim analysis is planned for this study.

4. ANALYSIS POPULATIONS

4.1. All-Enrolled Analysis Set

The All-Enrolled Analysis Set is defined as all patients who were enrolled in the study, whether dosed with rFIXFc or not. Patients will be considered enrolled when the Investigator has verified that they are eligible according to the criteria in Sections 8.1, 8.2 and 8.3 of the protocol.

Patient disposition summaries, enrollment summaries and all patient data listings will be based on the All-Enrolled Analysis Set, unless otherwise stated in this SAP.

4.2. Safety Analysis Set

The Safety Analysis Set is defined as all patients who received at least 1 dose of study rFIXFc. All analyses and summaries of safety, demographics, and baseline characteristics will be based on the Safety Analysis Set, unless otherwise specified in this SAP.

4.3. Full Analysis Set

The Full Analysis Set (FAS) is defined as all enrolled patients who receive at least 1 dose of study rFIXFc. All analyses and summaries of efficacy and exploratory endpoints will be based on the FAS, unless otherwise specified in this SAP.

5. DEFINITIONS AND DATA HANDLING

Study 998HB303 is being conducted under the sponsorship of Bioverativ Therapeutics Inc. Data management is being performed under contract with IQVIA in collaboration with Bioverativ. Statistical analysis will be performed by Bioverativ's Biostatistics Department and/or a designated contract research organization (CRO), using SAS® version 9.4 or higher and, where appropriate, additional validated software. This SAP is based on Version 3 of the approved study protocol dated 06 August 2018 and details the analyses to be performed and summaries to be produced for the final analyses for the Clinical Study Report (CSR).

5.1. General Principles

In general, the following approaches will be used in analysis/summary of baseline/demography, safety, efficacy and exploratory endpoint data, unless otherwise specified in this SAP.

No statistical hypothesis testing is planned. However, 95% confidence intervals (CIs) when determined for a binomial proportion will use the Clopper-Pearson method.

5.1.1. Data Presentation

In general, presentations of background/demography and safety data will include an overall/total column and those for efficacy and health outcome data will not. Any exceptions to this are specified in the relevant section.

There is only 1 treatment arm in the study. However, unless otherwise stated, all analyses and background/demography tables will be presented for the following treatment groups, as defined in Section 3.1.2:

- Patients who were ever on an episodic regimen
- Patients who were ever on a prophylactic regimen
- Patients who were ever on an ITI regimen

For longitudinal data, the safety or efficacy periods included for these groups is the time spent on that regimen within that period. These periods are defined in Section 5.3 and 5.4.

Selected tables will also be presented by patients' inhibitor development status, if there are at least 5 patients in the positive inhibitor subgroup (defined as in Section 5.2.4).

5.1.1.1. Continuous Variables

Continuous variables (e.g., age) will be summarized using the following standard summary statistics: number of patients (n), mean, standard deviation (SD), median, minimum value (min), and maximum value (max). In addition, if specified in the analysis table shells for this study, the 25th and 75th percentiles will also be presented. Summary statistics, excluding minimum and maximum, will be presented to one decimal place beyond that with which the study data were collected. For example, for data collected to no decimal place (e.g., 20 EDs), the mean and median will be presented to 1 decimal place and the SD to 2 decimal places. Minimum and maximum will be displayed as reported in the source data. If the measurements are transformed,

then the mean, median, SD, minimum, maximum of the transformed measurements will be presented with the appropriate precision.

Unless impractical within a table of analysis results, statistics will be aligned by the decimal place in the summary tables (even if not displayed in this manner in the table shells).

5.1.1.2. Categorical Variables

Categorical variables (e.g., adverse event) will be summarized using counts and percentages. All percentages will be rounded and presented to one decimal place, unless otherwise specified in the Statistical Programming Specifications for the study. The denominator for calculating percentages will depend on the variable to be summarized. For example, the denominator for calculating percentage of patients with any adverse event will be the Safety Analysis Set, which is number of patients dosed with rFIXFc.

5.1.1.3. Event Time Variables

The only such variable being analyzed in this study is the time to inhibitor (see Section 5.2.4 for complete definition). The cumulative incidence of these inhibitors over time (EDs) will be estimated using the Kaplan-Meier method and presented graphically.

5.1.2. Pooling Sites for Analysis

All sites will be pooled and reported together for analysis.

5.2. Study Definitions

5.2.1. Study Days

Study day for an event will be calculated from the first dose of study drug 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 study drug. Study Day -1 is the day immediately preceding Study Day 1. There is no Study Day 0 in this study. Study days will be included in the data listings where indicated on the listing shells. "NA" for "not applicable" will be used to indicate that a patient did not receive the respective study drug.

5.2.2. Baseline

Unless specified otherwise, for the purpose of analyses involving change from baseline during treatment with rFIXFc, baseline is defined as the last non-missing measurement (that can be used for data analysis i.e. was not taken during a surgical/rehabilitation period) taken prior to the first dose of study medication rFIXFc.

If a patient requires rescreening during the study, then baseline characteristics for the summary table will be taken from the first screening visit.

5.2.3. Visit Windows

Screening Visit

Screening assessments to determine subject eligibility for the study will be collected within 8 weeks after the first Screening Visit (i.e., the first visit for any activity other than informed consent, which can occur prior to the subject's birth). If more than 8 weeks elapse and screening activities have not been completed, the inhibitor and factor IX activity blood draws must be repeated. Other screening assessments that have not yet been completed must be completed within an additional 8 weeks.

Baseline Incremental Recovery Visit

Baseline IR Visit assessments are performed as soon as practicable once all eligibility criteria have been met and the patient has been enrolled. The Baseline IR Visit activities may be completed on the same day as Screening, or they may be completed as a part of a separate visit or at an unscheduled visit. Samples for IR calculations are taken when the patient is in a non-bleeding state, after at least a 72 hour washout.

Treatment Period Visits

Patients on episodic or prophylactic treatment in this study participate in regular interim visits for follow up, as well as follow up at specific ED milestones. Regular interim visits were every 12 (±2) weeks.

ED Milestone Visits

Unscheduled visits are performed at the following ED milestones to perform protocol-mandated inhibitor tests: 5 EDs (±2 EDs), 10 EDs (10-15 EDs), 20 EDs (20-25 EDs) and 50 EDs (50-55 EDs).

Surgery Visits

Surgery visits are as follows:

- Pre-Surgery Visit (Week -4 to Week -2). Not required for emergent surgery.

- Preoperative Assessment (Day of Surgery). If surgery is delayed by ≥8 weeks, preoperative assessments are to be repeated. These include assessments of FIX activity and Nijmegen-modified Bethesda assay. For minor surgery, the Investigator will be in contact with the patient or patient's parent/caregiver to determine when the patient should return to the regular pre-surgery regimen.

- Postoperative Visit (1 to 2 weeks after surgery). Visit is required for major surgeries only.

- Last Postoperative Visit. This visit occurs when the Investigator determines that the patient can return to the regular pre-surgery regimen and is not required if the return to the regular pre-surgery regimen occurs at the Postoperative Visit. If the subject is withdrawn from the study, then he will complete ET/EOS Visit assessments at least 2 weeks after surgery.

ITI Visits

After a patient on episodic or prophylactic treatment is confirmed as having high-titer inhibitors, or low-titer inhibitors with poorly controlled bleeding, the patient may participate in ITI visits. Pre-ITI assessment is on ITI Week 0. Interim ITI visits are every 4 weeks (± 2 weeks) from ITI Week 4 to Week 24, and subsequently every 12 weeks (± 2 weeks) from ITI Week 36 until End of Treatment (EOT).

End-of-Treatment Visit

End of Treatment (EOT) for individual patients is defined as follows:

- A patient who completes at least 50 EDs of rFIXFc and is not on an ITI regimen, is considered to have completed treatment.

- A patient undergoing ITI with rFIXFc is considered to have completed treatment if either of the following occurs:

    o The patient achieves successful immune tolerance as defined in protocol Section 10.2.6.

    o The patient completes 24 months on an ITI regimen without achieving successful immune tolerance.

- Individual patients may also have to end treatment because one of the following has occurred:

    o The patient meets the criteria for early withdrawal.

    o Study stopping rules are met.

    o EOS is reached.

Upon ending treatment for any of the reasons described above, the subject will return to the site for the ET/EOS visit.

Final Safety Follow-Up Visit

The Final Safety Follow-Up Visit (by telephone or in person) will be conducted within 14 (+7) days after the last dose of rFIXFc to assess the patient's status, collect AEs and/or SAEs, collect concomitant medications and procedures, and follow up on open AEs and SAEs.

5.2.4. Study-Specific Definitions

Exposure Day

One ED is defined as a 24-hour period in which a patient receives 1 or more doses of rFIXFc, with the time of the first injection of rFIXFc defined as the start of the ED.

Bleeding Episode

A bleeding episode is defined as follows: A bleeding episode starts from the first sign of a bleed, and ends no more than 72 hours after the last injection to treat the bleed, within which any symptoms of bleeding at the same location, injections ≤72 hours apart, are considered the same

bleeding episode. Any injection to treat the bleeding episode, taken >72 hours after the preceding one, will be considered the first injection to treat a new bleeding episode in the same location. Any bleeding at a different location is considered a separate bleeding episode, regardless of the time from the last injection.

Spontaneous Bleeding Episode

Bleeding episodes are classified as spontaneous if a parent/caregiver/patient records a bleeding event when there is no known contributing factor such as a definite trauma or antecedent "strenuous" activity. The determination of "strenuous" is at the discretion of the Investigator, and the parent/caregiver/patient will be instructed on this by the Investigator.

Traumatic Bleeding Episode

Bleeding episodes are classified as traumatic if the parent/caregiver/patient records a bleeding episode when there is a known or believed reason for the bleed. For example, if a patient exercises strenuously and then has a bleeding episode in the absence of any obvious injury, the bleeding episode will still be recorded as traumatic. Target joint bleeding episodes can be traumatic if a known action leads to bleeding into the joint.

High and Low Titer Positive Inhibitors

A positive inhibitor test result is defined as an inhibitor test result of ≥0.60 BU/mL that is confirmed by a second test result of ≥0.60 BU/mL from a separate sample, drawn 2 to 4 weeks following the original sample. Both tests must be performed by the central laboratory using the Nijmegen-modified Bethesda assay. The date of the inhibitor is the date of the sample with the first positive test result which was subsequently confirmed.

- A positive low titer inhibitor is defined as an inhibitor test and confirmatory test, both with results of ≥0.60 and <5.00 BU/mL.

- A positive high titer inhibitor is defined as an inhibitor test and confirmatory test, both with results of ≥5.00 BU/mL.

Patients with discordant inhibitor test results (initial low titer result followed by high titer result or initial high titer result followed by low titer result) should have repeat inhibitor testing performed by the central laboratory from a third separate sample, drawn 2 to 4 weeks following the previous sample.

- If 2 of 3 test results are <5.00 BU/mL, the inhibitor is considered low titer.

- If 2 of 3 test results are ≥5.00 BU/mL, the inhibitor is considered high titer.

5.2.5.   Subgroup Definitions

Surgery Subgroup

The Surgery Subgroup is defined as all patients who have undergone major surgery after first dose of study drug. This set will be described in the disposition table and all analyses and listings of major surgeries will be presented for this population.

Inhibitor Subgroups

Patients developing a positive inhibitor after exposure to rFIXFc will be included in Inhibitor Subgroup. Within this subgroup, there are several further classifications:

1. Patients with high-titer inhibitors, defined as in Section 5.2.4
2. Patients with low-titer inhibitors, defined as Section 5.2.4, that meet the below clinically meaningful criteria
3. Patients with low-titer inhibitors that do not meet the below clinically meaningful criteria

The delineation of clinically meaningful will be performed on a case-by-case basis via medical adjudication prior to the final analyses, based upon the data available for the analysis. This assessment will take account of relevant clinical factors, including but not limited to:

- Entry to the ITI regimen
- Any bypassing or immunomodulatory agents received up to 4 weeks before inhibitor development and any time after
- Withdrawal from the study due to complications assessed as related to inhibitor development
- Any SAE of a bleeding event up to 4 weeks before inhibitor development or any time after
- A pattern of non-serious treated bleeding events which require a change in study drug (rFIXFc) regimen

By definition, all high-titer inhibitors are clinically meaningful, as patients with high-titer inhibitors must either enter the ITI sub-study or withdraw.

ITI Subgroup

The ITI Subgroup is defined as all patients who consent to and initiate the ITI treatment regimen (see Section 3.1.2.3). This set will be described in the disposition table and all analyses and listings of data from the ITI regimen will be presented for this population when applicable.

5.2.6.   End of Study

The end of the study (EOS) will occur after at least 20 patients have reached at least 50 EDs with rFIXFc. Once this milestone has been achieved, all ongoing study patients will return to the study center for their final visits.

5.3.   Treatment Regimens for Analysis

For the purpose of analysis, the treatment regimen means the actual treatment regimen(s) that the patient follows over the course of the study (i.e., not necessarily the regimen they started on). For example, a patient who starts the study on the episodic regimen and switches to a prophylactic regimen will appear in the summaries of both the episodic and the prophylactic regimens based on the time he spent in the respective regimens.

5.3.1.   Start Date and Time of the First Treatment Regimen

The start date and time of the first treatment regimen is defined as either:

- The date and time of the first rFIXFc dose for patients beginning on a prophylactic treatment regimen, as per the treatment assignment eCRF data.

- The date and time 120 hours after the date and time of the baseline PK dose for patients beginning on an episodic treatment regimen, as per the treatment assignment eCRF data.

5.3.2.   End Date and Time of the Last Treatment Regimen

The end of the last treatment regimen will be either:

- The date and time of the last rFIXFc dose for patients whose last treatment regimen was prophylaxis, ITI, or if they ended the study in a surgical/rehabilitation period.

- At 23:59 on the day of the last non-safety follow-up study visit for patients whose last treatment regimen was episodic.

5.3.3.   Treatment Regimen Changes

In the following sections, new treatment regimen refers to the regimen to which the patient has changed, and the previous treatment regimen refers to the regimen immediately before the new treatment regimen. The start date and time of the new treatment regimen and the end date and time of the previous treatment regimen are defined in the following scenarios:

- From an episodic regimen to a prophylactic regimen: The prophylactic regimen starts at the date and time of the first prophylactic dose in the prophylactic regimen. The episodic regimen ends 1 minute before that. If the time of the first prophylactic dose in the prophylactic regimen is not available, the prophylactic regimen will start at 00:01 on the day of the first prophylactic dose in the prophylactic regimen, and the episodic regimen will end at 23:59 on the day prior to that.

- From a prophylactic regimen to an episodic regimen: The prophylactic regimen ends at the date and time of the last prophylactic dose in the prophylactic regimen. The episodic regimen starts 1 minute after that. If the time of the last prophylactic dose in the prophylactic regimen is not available, the prophylactic regimen will end at 23:59 on the day of the last prophylactic dose in the prophylactic regimen, and the episodic regimen will start at 00:01 on the next day.

- From an episodic regimen to an ITI regimen: The ITI regimen starts at the date and time of the first ITI dose in the ITI regimen. The episodic regimen ends 1 minute before that. If the time of the first ITI dose in the ITI regimen is not available, the ITI regimen will start at 00:01 on the day of the first ITI dose in the ITI regimen, and the episodic regimen will end at 23:59 on the day prior to that.

- From a prophylactic regimen to an ITI regimen: If there is no prophylactic dose on the day of the treatment regimen change recorded in the eCRF, the ITI regimen starts at

00:01 on the day of treatment regimen change, and the prophylactic regimen ends at 23:59 on the day prior to the day of treatment regimen change. If there is a prophylactic dose on the day of treatment regimen change, the ITI regimen starts 1 minute after that prophylactic dose, and the prophylactic regimen ends on the date and time of that prophylactic dose.

5.3.4. Duration of a Treatment Regimen

The duration of a given treatment regimen is the time period from the start of the treatment regimen to the end of that treatment regimen. The duration will stop and start for each treatment regimen change. If a patient is treated in a given treatment regimen more than once, the total durations in the same treatment regimen will be added together. For example, if a patient is treated with the prophylactic regimen and then undergoes surgery and then goes back to the prophylactic regimen, then his total duration in the prophylactic regimen will be the sum of the two durations in the prophylactic regimen. Further details will be provided for individual analysis where needed.

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

5.4. Study Periods

5.4.1. Screening Period

The screening period starts after a patient signs the study consent form and ends immediately prior to administration of the first dose of study drug rFIXFc.

5.4.2. Efficacy Period

The efficacy period will be used for the evaluation of efficacy and health outcome endpoints. For a patient to have an evaluable efficacy period over the duration of study, he must have at least 1 day of treatment for an episodic regimen or at least 2 prophylactic injections for prophylactic regimens.

The start and end, and the total duration of the efficacy period for a given treatment regimen is the same as the start and end, and the total duration of that treatment regimen defined in Section 5.3.4 with the exceptions described in the following two subsections. The start of the efficacy period for each patient is the start of their first treatment regimen and the end is the end of their last.

5.4.2.1. Adjustments Due to Surgical/Rehabilitation Periods

For analysis purposes, the efficacy period for a given treatment regimen will be adjusted for all surgical/rehabilitation periods (major and minor). The start and end of the efficacy period for a given treatment regimen are adjusted as follows:

- For patients on a prophylactic regimen before the start of a surgical/rehabilitation period, the efficacy period for the prophylactic regimen continues up to the last dose (for prophylaxis or bleeding) before the start of the surgical/rehabilitation period.

- For patients on the episodic regimen before the start of a surgical/rehabilitation period, the efficacy period for the episodic regimen continues up to 1 minute before the start of a surgical/rehabilitation period.

- For patients on a prophylactic regimen following the end of a surgical/rehabilitation period, the efficacy period for the prophylactic regimen starts or re-starts at the first prophylactic dose following the end of the surgical/rehabilitation period.

- For patients on the episodic regimen following the end of a surgical/rehabilitation period, the efficacy period for the episodic regimen starts or re-starts at 00:01 on the day following the end of the surgical/ rehabilitation period.

Start and end dates/times for the efficacy period for given treatment regimens and treatment regimen changes will be adjusted for each surgery (major or minor) as necessary.

For patients on a prophylactic regimen before the start of a surgical/rehabilitation period, the interval of time between the last dose before the surgical/rehabilitation period and the start of the surgical/rehabilitation period will not be attributed to the efficacy period for the prophylactic regimen. By definition, there should not be any treated bleeding episodes in this interval of time.

For patients on a prophylactic regimen following the end of a surgical/rehabilitation period, 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 (ABR).

5.4.2.2. Adjustments Due to Large Injection Intervals

For analysis purposes, the efficacy period will also be adjusted to account for large intervals between injections resulting from missing data. A large interval is defined as >28 days between any 2 adjacent rFIXFc injections within a prophylactic treatment regimen and any such intervals will be removed from the efficacy period. The efficacy period prior to each such interval will end at the time of the first injection of this interval and restart (or start if it is the first interval of a treatment regimen) at the time of the second injection of this interval. The efficacy period will be adjusted for each identified interval that is not within a surgical/rehabilitation period. This algorithm applies only to prophylactic regimens and no adjustment for large injection intervals will be made for episodic treatment regimens.

5.4.3. Surgical/Rehabilitation Period

The broadest span of time for the surgical/rehabilitation period is from the first dose of rFIXFc 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 postoperative care/rehabilitation. Since not all patients 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 is a prophylaxis dose or dose given for "OTHER" reason prior to the surgery on the day of or the day before surgery, the last of these doses should be selected.

- If there is no pre-surgical dose or a prophylactic 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 regular 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 the patient is not on prophylactic regimen following the surgical/rehabilitation period (e.g., the patient is on episodic regimen after completing the surgical/rehabilitation period, or the patient simply received no further prophylactic doses), then the end of the surgical/ rehabilitation period is:

  o Imputed as 23:59 on the last date among the dates for discharge from the hospital, post-operative visit 1, post-operative visit 2, and the end of rehabilitation.

  o If all of the dates mentioned above are missing, then the select the date of the end of surgery 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 the overall end of study is declared while the patient 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.

Two 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. The same will also apply among overlapping minor surgeries.

- 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 or

recorded as 00:00. The surgical/rehabilitation period for the major surgery will include the minor surgery (i.e., the surgical/rehabilitation period for the major surgery does not stop and restart around the minor surgery) and will end as otherwise defined.

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

5.4.4. ITI Period

The ITI period is defined as the time from when a patient in the ITI sub-study begins this treatment regimen until they complete or withdraw from the study. The start of this period is the date and time of the first dose of the ITI regimen.

5.4.5. Safety Period

The overall safety period is defined as beginning at the first dose of study medication rFIXFc. For patients who are subsequently enrolled, the safety period ends on the date of the Final Safety Follow-up Visit (by telephone or in person), 14 (+7) days after the last dose of rFIXFc. For patients who fail screening, this period ends on the date that this is confirmed.

The safety period on a specific treatment regimen is as described in Section 5.3 except that the end of the patient's last treatment regimen is the end of their safety period.

5.4.6. Pharmacokinetic Period

There is no defined PK period in this study.

5.4.7. Follow-up Period

The follow-up period is defined as the period 14 (+7) days after the last dose of rFIXFc.

5.5. 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 lapse between 2 consecutive injections administered to treat bleeding. Details are provided in Section 7.4.1.

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 9.3.1, respectively.

For patients in the ITI Subgroup, determination of response requires baseline IR. If this is missing, an absolute value is employed. Further details can be found in Section 7.4.9.

5.6. Electronic Patient Diary (EPD) Data

Patient recorded diary data was within this project, previously queried via a defined process which required confirmation with the patient of all changes. Taking into consideration audit findings and industry standards to control changes to patient reported data, the query process was updated to allow only changes defined as not requiring patient confirmation. No changes which were not allowable under this new process were made to the EPD data. Although consolidation of records of single vials recorded within 60 minutes of each other (SVC/L60) was classified as a change not requiring patient confirmation (as agreed with MHRA in 2014), these changes are no longer being made directly into the data, but will be applied via a programmatic data convention. In addition, true duplicate records resulting from administrative issues and hence not requiring patient confirmation of the change will be deleted. The exception to this is where both injections are in the eCRF, which do not require patient confirmation, as site notes provide an alternative source and so these can be queried and processed as per the previous process.

These programming algorithms to address these two scenarios are described as follows:

1) Record consolidation:

When a dose requires more than one vial and these vials are erroneously recorded in the EPD/eCRF as separate injections, albeit within a short time window, the change to consolidate these multiple records into one record is called Single Vial Consolidation (SVC). Based on the EPD set up, the programming algorithm to identify and consolidate the records is as follows:

- Identify all injection records within 60 minutes of one another where the variables (injection date/times, lot numbers, number of vials, and vials strength in nominal IU) are not exactly the same on each record. There are four scenarios:

    - Date and time of injections are not exactly same, and lot numbers, number of vials, and vials strength in nominal IU are not the same.

    - Date and time of injections are not exactly same, but lot numbers, number of vials, and vials strength in nominal IU are the same.

    - Date and time of injections are exactly same, but lot numbers, number of vials, and vials strength in nominal IU are not the same.

    - Date and time of injections are exactly same, and lot numbers, number of vials, and vials strength in nominal IU are the same, and these duplicates occurred for reasons which cannot be attributed to administrative issues as specified below.

- Consolidate injections as follows:

    - Record with earliest injection date/time retained with corresponding contextual information.

    - Combine/sum values related to the dose (e.g. lot numbers, number of vials, volume injected, nominal and actual dose) into the single retained record.

If injections identified with the above algorithm have distinctly different reasons (e.g., one injection is recorded as bleeding or surgery and another is recorded as prophylaxis, additional, or OTHER), then the records should NOT be consolidated. However if one reason is missing, then consolidation can be performed.

2) True duplicates removal:

When injections are identified in the EPD with exactly the same date/times, lot numbers, number of vials, and vials strength in nominal IU, these may have resulted due to administrative issues and are therefore true duplicates. There are three types of administrative issues as follows:

- Technical transmission issue

- Entry of same record into 2 different devices

- Records duplicated in EPD and eCRF which remain despite attempts to correct the data via the query process

The programming algorithm to identify and delete the duplicates is as follows:

- Identify all injections that have exactly the same date/times, reasons for injection, lot numbers, number of vials, and vials strength in nominal IU

- Remove the duplicates and keep a single record

As with SVC, if injections identified as duplicates have distinctly different reasons (e.g., one injection is recorded as bleeding or surgery and another is recorded as prophylaxis, additional, or OTHER), then these cannot be considered duplicates and removed. However if one reason is missing, then they can be considered duplicates and removed.

6.   STUDY PATIENTS

Unless otherwise specified, all tables in this section will be presented by the treatment regimen groups described in Section 5.1.1.

6.1.   Disposition of Patients

Patient disposition will be presented by treatment regimen as described in Section 5.1.1.

This table will present the number and percentage of patients in the Safety Analysis Set and the All-Enrolled Analysis Set. Percentages will be based on the total number of patients who were enrolled in the study, or who received at least 1 dose of rFIXFc.

In addition, the number and percentage of patients in the Full Analysis Set (FAS) and in the FAS with an efficacy period, as well as those in the Surgery Subgroup, the Inhibitor Subgroups, and the ITI Subgroup, will be provided. The number and percentage of patients who completed/ discontinued the study, including the primary reason for those who discontinued, will be tabulated. Percentages will be based on the number of patients in the All-Enrolled Analysis Set.

Patient disposition, including the date of the last visit and the reason for early termination or early withdrawal for patients who did not complete the study, will be provided in a data listing.

The number and percentage of patients enrolled will be summarized by country and site, for the All-Enrolled Analysis Set.

The number of patients attending each key study visit will be summarized by key study visit overall for the Safety Analysis Set, including visits in the main study. If the ITI Subgroup consists of at least 5 patients, this summary will also be performed for the ITI Subgroup, including only visits in the ITI period.

6.2.   Demography and Baseline Disease Characteristics

Demographics and baseline characteristics will be summarized for the Safety Analysis Set. Demographics and baseline characteristics will be summarized as continuous variables and as categorical variables, as appropriate.

6.2.1.   Demography

Demographic characteristics include age, height and weight at screening plus sex, race, ethnicity, and geographic location. Geographic locations are defined as Europe, North America, and other. Europe includes Belgium, Denmark, France, Germany, Ireland, Italy, the Netherlands, Poland, Spain, Sweden, Switzerland, and the United Kingdom. North America includes the United States. Other countries include Australia and New Zealand.

Age will be obtained from the interactive voice and web response system (IXRS) to avoid calculation errors arising from not having the day of the month for birth dates in the eCRF. Age will be summarized both as a continuous variable using descriptive statistics and categorically with the age categories representing each year from <1 through 17. This table will be presented by treatment regimen as described in Section 5.1.1.

6.2.1.1. General Medical and Surgical History

Medical and surgical history will be summarized by body system. A patient is counted only once if they report more than one occurrence in the same body system.

6.2.2. Baseline Disease Characteristics

6.2.2.1. Hemophilia History

Time since diagnosis of hemophilia will be summarized with descriptive statistics. The screening FIX activity values will be summarized categorically (<1%, ≥1%). Categorical summaries will also be provided for FIX genotype, family history of inhibitors, vaccination within last year, HIV status, Hepatitis B status, and Hepatitis C status.

6.2.2.2. Bleeding History

Patients' total estimated bleeding episodes (spontaneous plus traumatic) within the last 3 months prior to study screening will be summarized categorically (0, 1-2, 3-5 and >5 and with descriptive statistics). Percentages for the categorical summaries will be based on the number of patients who provided data. Total estimated bleeding episodes in the 3 months prior to study screening will also be summarized for the number of spontaneous and traumatic bleeding episodes using descriptive statistics.

6.2.2.3. Family Hemophilia History

No family history of hemophilia is collected in this study. Family history of inhibitors to FIX is referenced above in Section 6.2.2.1.

6.2.2.4. Risk Factors for Inhibitor Development

The following risk factors will be summarized for patients in the Inhibitor Subgroup and those not, as specified in Section 5.2.5:

- Race - black or African American or white Hispanic / other, from demography data

- Family history of inhibitor - Y/N, as per hemophilia history data

- Vaccination - Y/N, as per hemophilia history data and concomitant medications prior to date of inhibitor development

- FIX genotype - to be delineated based upon final data according to the following guidelines for all genotypes that fall under the general categories of:
    - High risk – large deletions or nonsense variants
    - Low risk – small deletions/insertions, missense variants, or promoter/regulatory region mutation
    - Unknown/missing

- TEAE of infection prior to date of inhibitor development - Y/N, derived from adverse event data based upon events with MedDRA SOC Infections and Infestations

- Major surgery during study prior to date of inhibitor development   - Y/N

6.3. Physical Examination

The number and percentage of patients with physical examination abnormalities at screening will be presented by body system. Percentages will be based on the number of patients for whom a screening physical examination is available. On-treatment physical examination findings will be listed.

6.4. Non-study Drug Medications

6.4.1. Prior and Concomitant Medications

Prior and concomitant medications relative to rFIXFc will be summarized for the Safety Analysis Set. Summaries will be based on the number and percentage of patients taking medications by WHODrug standardized medication text. Within each WHODrug standardized medication text a patient 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 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 EOS visit and the other for medications taken after the 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 rFIXFc. Prior medications are all drugs and substances taken before the first rFIXFc dose was received. Concomitant medications are those administered during or after the first injection of rFIXFc while on study, or administered prior to the first administration of rFIXFc and ongoing at the start of rFIXFc 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 rFIXFc. Medications reported for a patient will be classified as concomitant unless they can be excluded as such, as follows:

- A medication that is started prior to the first dose of rFIXFc and was ongoing during and/or after the first dose of rFIXFc 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 rFIXFc and the concomitant medication stop date is before the start day of the first dose of rFIXFc, 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 rFIXFc 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 rFIXFc and the stop date is before the start date of the first dose of rFIXFc, then the medication will be classed as prior only.

In this study, for patients who receive breast milk, maternal concomitant medications are also collected at the same time points as other concomitant therapies, unless the breast milk is derived from a source other than the mother or the mother did not consent. These will be presented in separate listings, but in a similar way, to other concomitant medications.

Prior and concomitant medication will be coded using WHODrug-enhanced dictionary version from March 2017.

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. Protocol Deviations

Protocol deviations will be recorded throughout the study or in the case of deviations based upon data entered in the EPD, monitored throughout the study and finalized at the end (more details in the Programmatically-Defined Protocol Deviations Criteria document). Major and minor protocol deviations/violations are to be pre-specified prior to database lock, as per the guidance provided in the study Clinical Operations Plan document.

The number of patients with major protocol deviations will be summarized for the Safety Analysis Set and also including only deviations that affect efficacy, to be identified prior to database lock. Major protocol deviations that occurred during a surgical/rehabilitation period will be presented separately in the summary. A data listing of all protocol deviations, major and minor, will be provided.

6.6. Study Drug

Study treatment is described in Section 3.1.2. Study drug administered will be listed by patient for the FAS. This will include the reason for administration (PK assessment, episodic (treatment of a bleeding episode), prophylaxis, ITI, surgery, other), date and time of administration, dose and dosing intervals, consumption and compliance. It will also include lot number and nominal potency of the lots used.

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 patient's most recent weight in kg prior to the dose of study drug.

PK doses are all 50 IU/kg at the Baseline IR Visit and the ITI regimen IR assessments, and are calculated using the actual potency of the vial (between 80 to 125% of nominal strength) and using partial vials where necessary. Therefore PK doses in the analysis are similarly calculated using the exact number of complete and partial vials, the volume and actual potency of each vial and the patient's most recent weight.

Both types of dose are calculated as follows:

$$\text{Dose (IU/kg)} = \frac{\left(\dfrac{\text{Total volume administered}}{\text{Volume of vial}}\right) \times \text{Actual/Nominal Potency of Vial}}{\text{Weight (kg)}}$$

PK doses are not used for the purpose of preventing or treating bleeding and therefore the total annualized rFIXFc consumption will exclude the IU/kg amount that is used for PK doses. However, data collected over the time in which the PK dose was administered will be included in the safety analyses.

6.6.1. Exposure

6.6.1.1. Number of Injections and Exposure Days to rFIXFc

For any patient, the total number of days of exposure to rFIXFc will be accumulated from the time of their first on-study injection of rFIXFc. An ED is a 24-hour period in which one or more rFIXFc 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 rFIXFc for each patient will be summarized categorically (<5, 5-<10, 10-<20, 20-<50, 50-<75, 75-<100 and >=100) and with descriptive statistics for the Safety Analysis Set.

The total number of injections per patient will be summarized overall and by reason for injection (prophylactic regimen, ITI regimen, spontaneous bleed, traumatic bleed, follow-up injection, surgical and other) using descriptive statistics for the Safety Analysis Set.

These tables will be presented by treatment regimen as described in Section 5.1.1.

The total number of injections and EDs will also be summarized by EPD entry compliance (see Section 6.6.2.3), <80% and >=80%, where >=80% is considered compliant.

6.6.1.2. Duration of rFIXFc Dosing

For any patient, the duration of rFIXFc dosing for a given treatment group (episodic, prophylactic, and ITI) will be calculated from the start date/time of the starting regimen to the end date/time of the last regimen in that treatment group, as defined in Sections 5.3.1 and 5.3.2. The duration of overall rFIXFc dosing will be calculated from the date/time of the first rFIXFc dose, to the end date/time of the last treatment regimen in the study. Any interruptions to dosing will not be accounted for when calculating this duration.

The number and percentage of patients whose duration of dosing was at least 13, 26, 39, 52, 65, 78, 91, 104, 117 and 130 weeks (2.5 years) will be summarized based on the integer part of the calculated week nominal for the Safety Analysis Set.

Duration of rFIXFc dosing (weeks) will also be summarized using descriptive statistics for the Safety Analysis Set. Weeks will be represented in the descriptive statistics as if these were data collected with 1 decimal place.

These tables will be presented by treatment regimen as described in Section 5.1.1.

Duration of rFIXFc dosing will also be summarized by EPD entry compliance (see Section 6.6.2.3), <80% and >=80%, where >=80% is considered compliant.

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

The prescribed prophylactic dose and dosing frequency will be summarized descriptively for the prophylactic and ITI treatment periods.

Because dosing in this study is based on variable doses and dosing intervals, average weekly dose ▓▓▓▓▓▓▓▓▓▓▓▓▓▓▓▓▓▓▓▓ and average dosing interval will be derived for each patient to characterize the amount of rFIXFc received for prophylaxis. Descriptive statistics will be provided using the FAS.

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 major surgical/rehabilitation period. Data to be included in the calculations, specifically the prophylactic doses and the total duration of prophylactic treatment, will come strictly from intervals representing two consecutive prophylactic doses (PR) during the efficacy period (see Section 5.4.2 for a description of the efficacy period). The sum of doses at PR_x and the sum of interval durations ($PR_{x+1} - PR_x$), 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.

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

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

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

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 patient 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) and with descriptive statistics.

6.6.1.4. Consumption

The total annualized rFIXFc consumption (IU/kg) will be calculated for each patient using the following formula:

$$\text{Annualized consumption} = \frac{\text{Total IU/kg of rFIXFc during the efficacy period}}{\text{Total number of days during the efficacy period}} \times 365.25$$

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

Total annualized rFIXFc consumption per patient will be determined for the efficacy period (i.e., excluding the PK assessments and surgery/rehabilitation periods [major surgeries]). Total annualized consumption per patient will also be derived based on treatment regimen and overall.

Consumption is a secondary endpoint in this study. A description of how consumption will be summarized is described in Section 7.4.7.

6.6.1.5. Last Prescribed Dose

For patients on a prophylactic regimen at any time during the study, the last prescribed dose and dosing frequency will be summarized as a cross tabulation of dosing frequency by dose (IU/kg) in which the number and percentage of patients who were last prescribed each combination of dose and dosing frequency (as applicable) will be tabulated. The last prescribed dose will also be summarized for each dosing frequency using descriptive statistics. If no dose (dosing frequency) changes were prescribed, then a patient's starting dose (dosing frequency) will be used. The dose for the twice weekly regimen will be the average of the two doses given. Percentages will be based on the number of patients in each prophylactic regimen (i.e., not on the number of patients in each dosing frequency category). This analysis will not include the ITI period and last prescribed dose for these cases is that before the commencement of ITI.

6.6.2. Compliance

Dose compliance will be assessed during the efficacy period and will be summarized for the FAS. Except for doses administered in the clinic, study treatment may be administered by a caregiver. Data from the eCRF and EPD will be considered for the analysis of treatment received and patients' compliance with the study protocol.

6.6.2.1. Compliance in the treatment of bleeding episodes

Bleeding episodes are defined in Section 5.2.4. All bleeding episodes during the efficacy period for which there is a date and time for both the onset of the bleeding and treatment of the bleeding will be evaluated for compliance. Compliance will first be determined on a per-bleed basis and then on a per-patient basis. That is, compliance for each bleeding episode will be determined and then the overall percentage of bleeding episodes for which treatment was in compliance will be determined for each patient.

The definition of compliance for the treatment of an individual bleeding episode, as specified by the Sponsor, is no more than 8 hours between the onset of the bleed and the initiation of treatment for the bleed. Thus, the compliance rate for the treatment of bleeding episodes will be measured by determining the proportion of injections administered within a maximum of 8 hours of the initial sign of a bleed, as follows:

$$\text{Treatment of bleed compliance rate} = \frac{\text{Number of first injections to treat a bleed taken within 8 hours of the first sign of a bleed}}{\text{Total number of evaluable bleeding episodes}} \times 100$$

The following circumstances result in a bleeding episode being considered not evaluable for the determination of this compliance rate:

- The type of bleed has been classified as Unknown based on the definition of a bleeding episode (>72 hours between consecutive injections) since there is no onset time
- A missing bleed time for a spontaneous or traumatic bleed
- A bleed time that was recorded as being after the time of treatment

Descriptive statistics for compliance to treat a bleeding episode will be presented for the FAS.

6.6.2.2. Compliance of Prophylactic Injections

The compliance rate of each patient to the prescribed prophylactic and ITI dosing regimens during the efficacy 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-patient 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 patient.

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%-125% of the prescribed dose. An individual dosing interval will be considered compliant if the time between two prophylactic doses is within 36 hours of the prescribed dosing interval. Prescribed dose and dosing intervals are according to the Investigator. Instructions provided to the patient 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 patient.

The actual dosing intervals will be calculated as the length of time between consecutive prophylactic doses (date/time of PR_{x+1} – date/time of PR_x), PR_{x+1} and PR_x. 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 ≤ 1.5 day (+/- 36 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 5.4, will be used to evaluate prophylactic interval compliance. Dose and dosing interval compliance rates per patient will be determined as follows:

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

where the percentage of a prescribed dose is calculated as: (nominal dose taken/prescribed dose) ×100 and the "nominal dose taken" will be determined from the nominal potency labeled on the vials used by the patient for each injection of rFIXFc.

$$\text{Dose interval compliance rate} = \frac{\text{Number of doses taken within +/- 36 hours ███████████████ of prescribed day/time}}{\text{Total number of intervals}} \times 100$$

A patient is considered "dose compliant" or "dosing interval compliant" if his respective rate is at least 80%.

Descriptive statistics of the percentage of nominal doses taken per patient within 80%-125% range for dosing compliance as well as frequencies for the dose compliance rate (<80%, ≥80%) will be presented for the FAS. Similarly, descriptive statistics of the percentage of doses taken per patient within ±36 hours ████████████████ of the prescribed day as well as frequencies of the dosing interval compliance rate (<80%, ≥80%) will be presented for the FAS.

Based on their per-patient compliance rates for dose and dosing interval (each <80%, ≥80%), patients will be further classified into the following mutually exclusive categories for overall compliance to their prophylactic treatment as:

- Both dose and interval compliant

- Dose compliant or interval compliant (but not both)

- Neither dose nor interval compliant

6.6.2.3.   Compliance of EPD Contemporaneous Data Entry

Injections must be entered into the EPD within 7 days from the date of the injection. Injections entered outside the 7-day window will be reported as protocol deviations. Descriptive statistics of the percentage of the patients with fewer than 80% of their total individual EPD records entered within this 7-day window and those with ≥80% of records meeting this criteria will be presented for the FAS as well as a summary of % compliance to this criteria by patient.

7. EFFICACY ANALYSIS

7.1. General Efficacy Principles

Efficacy analyses will be based on the Full Analysis Set and unless otherwise specified, presented by the treatment regimen groups described in Section 5.1.1.

Additionally, the general efficacy and surgical/rehabilitation periods are defined in Section 5.4. Data on bleeding and rFIXFc consumption will be based on the efficacy period; surgical evaluations will be based on the surgical/rehabilitation period.

Analysis of efficacy endpoints that are visit-based will include data from all study visits whether or not in the efficacy period, unless that visit is coincidental with a surgical/rehabilitation period for a major surgery, in which case it would be excluded.

7.2. Multiplicity

Multiplicity is not a concern in this study since no statistical tests are being performed on the efficacy endpoints.

7.3. Analysis of Primary Endpoint(s)

All efficacy endpoints are secondary. Therefore, there will be no analysis of a primary efficacy endpoint.

7.4. Analysis of Secondary Endpoints

7.4.1. Bleeding Episodes

Bleeding episodes will be recorded in both the EPD and eCRF; this information will be used to derive the secondary efficacy endpoints. During the course of the study the Investigator is given the opportunity to disagree with the type of bleeding (spontaneous, traumatic) as classified by the patient/caregiver, and the patient/caregiver is subsequently given the opportunity to agree or disagree with the reclassification. If the patient/caregiver agrees with the Investigator's assessment, then all analyses subset by type of bleeding will be based on the Investigator's determination of the bleeding type whether or not the change was made to the patient's records.

Standardized definitions of bleeding episodes are provided in 5.2.4.

Bleeding episodes of an unknown type will be included in the determination of the annualized bleeding rate and in summaries based on bleeding episodes but, unless specified otherwise, will not be included in summary tables where endpoints are summarized by type of bleed.

7.4.2. Summary of Bleeding Episodes

As a description of the raw data collected in this study, the unadjusted number of bleeding episodes per patient will be summarized using descriptive and categorical (e.g. 0, >0-5, >5-10, >10-15, etc.) statistics over all bleeding episodes. Of note, the number of patients with a bleeding

episode for which the location is unknown will be tabulated in these summaries but no further analysis of unknown bleeding locations is planned.

The total patient years followed during the efficacy period (summed over all patients overall) will be provided in order to put the unadjusted numbers in perspective.

These summaries will be further broken down by bleed type and location. These tables will be presented by treatment regimen as described in Section 5.1.1.

7.4.3. Annualized Number of Bleeding Episodes per Patient (ABR)

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

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

The ABR will be summarized using descriptive and categorical (e.g. 0, >0-5, >5-10, >10-15, etc.) statistics for the FAS. All types of bleeding episodes (spontaneous, traumatic, and type unknown) will be included in determining the annualized number.

These tables will be presented by treatment regimen as described in Section 5.1.1.

This analysis will also be presented by the following subgroups:

- Patients with at least 50 EDs to rFIXFc within a treatment regimen

- Patients with at least 26 weeks of rFIXFc dosing within a treatment regimen

- History of bleeding (estimated frequency of bleeds in prior 3 months: 0, 1-2, 3-5 and >5)

- Patients with no major protocol deviations potentially impacting efficacy (see Section 6.5)

7.4.4. Annualized Number of Bleeding Episodes per Patient by Type and Location of Bleed

For completeness, summaries of the ABR will also be provided for the following subsets of bleeds for the FAS:

- Type of bleeding (spontaneous, traumatic, unknown)

- Location of bleeding (joint, muscle, internal, skin/mucosa)

  For the purpose of analysis bleeding episodes with a location of iliopsoas will be treated as a muscle bleed; however, the location will be displayed as iliopsoas in the listings.

- Location and type of bleeding (joint spontaneous, joint traumatic, muscle spontaneous, muscle traumatic, internal spontaneous, internal traumatic, skin/mucosa spontaneous, skin/mucosa traumatic)

These tables will be presented by treatment regimen as described in Section 5.1.1.

7.4.5. Assessment of Response to Treatment with rFIXFc for Bleeding Episodes Using the 4-Point Bleeding Response Scale

Using the EPD, each patient's parent/caregiver rates the treatment response to any bleeding episode using a 4-point scale. Ratings of treatment response are made approximately 8 to 12 hours from the time the injection is given to treat the bleeding episode and prior to any additional doses of rFIXFc given for the same bleeding episode. Response is also assessed by the Investigator and recorded on the eCRF for those patients who are treated in the hospital with rFIXFc for major bleeding episodes.

The 4-point scale is as follows:

- Excellent
- Good
- Moderate
- None

Response categories of excellent and good will be presented combined as well as individually. The number and percentage of injections in each response category will be tabulated based on all injections. Two summaries will be provided. In the first summary percentages will be based on the total number of injections administered for bleeding episodes for which a response was provided. In the second summary percentages will be based on the total number of bleeding episodes whether or not a response was provided.

The assessment of response will also be summarized on a per bleed basis by presenting the number and percentage of first injections to treat a bleeding episode for which the response to the treatment was categorized as excellent, good, moderate, or no response, using both approaches to determine the percentages.

The patient's assessment of response will be summarized for the FAS. In order to evaluate if there is a relationship between compliance to treat a bleed and response to the treatment of the bleed, this endpoint will additionally be summarized by compliance to treat the bleed where compliance will be based on the individual bleeding episodes.

These data will be provided in a listing which will include the total number of bleeding episodes and the number of first injections for which a response assessment was provided.

7.4.6. Total Number of EDs per Patient

The total number of EDs on rFIXFc for each patient will be summarized. This analysis is described in Section 6.6.1.1.

7.4.7. Total Annualized rFIXFc Consumption per Patient for the Prevention and Treatment of Bleeding Episodes

Total annualized rFIXFc consumption per patient for the prevention and treatment of bleeding episodes will be summarized for the FAS using descriptive statistics. See Section 6.6.1.4 for details on the annualized rFIXFc consumption derivation.

This table will be presented by treatment regimen as described in Section 5.1.1.

7.4.8. Number of Injections and Dose per Injection of rFIXFc Required 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-patient 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-patient basis. See Section 7.4.1 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 number of injections required for the resolution of a bleeding episode will be summarized across all bleeding episodes both categorically (1, 2, 3, 4, >4; 1, >1; and ≤2, >2) and with descriptive statistics. The average dose per injection and total dose required for resolution of a bleeding episode will be summarized using descriptive statistics.

Per patient: 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 patient. The average number of injections required for resolution of a bleeding episode will be summarized both categorically (1 to <2, 2 to <3, 3 to <4, and ≥4; and 1 to <2, ≥2) and with descriptive statistics. The averages for the per-patient average dose per injection and total dose required for resolution of a bleeding episode will be summarized using descriptive statistics.

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.

For the above analysis, data from the FAS will be summarized. These tables will be presented by treatment regimen as described in Section 5.1.1.

7.4.9. Response to Immune Tolerance Induction (ITI)

Response to the ITI treatment regimen will be analyzed for the ITI Subgroup of the Full Analysis Set if the ITI Subgroup consists of at least 5 patients. Possible treatment responses are:

Success

[redacted]

- [redacted]
  [redacted]
- [redacted]
  [redacted]
  [redacted]

[redacted]
[redacted]
[redacted]

- [redacted]
  [redacted]
- [redacted]
  [redacted]
- [redacted]
  [redacted]

Failure:

ITI failure is defined as the inability to meet criteria for Success after 24 months on ITI.

Early Withdrawal/ITI Ongoing:

Patients may withdraw from the study during the ITI period before reaching 24 months or Success. In addition, any patients still in the ITI sub-study at the time of EOS will be included in this category.

Response categories of success, failure, early withdrawal, and ITI ongoing will be presented overall for the ITI Analysis Set, and separately for the inhibitor subgroups specified in Section 5.2.5, namely:

- Patients with high-titer inhibitors
- Patients with low-titer inhibitors that meet the clinically meaningful criteria

A data listing will be generated for all patients in the ITI sub-study. This will include date of first inhibitor sample with a positive result, all inhibitor and IR measurements after commencement of ITI therapy, as well as dosing information. It will also include elapsed time to each assessment and a flag to indicate the patient's ITI status.

7.5. Analysis of Exploratory Endpoint(s)

7.5.1. Health Outcomes

The health outcomes related to hemophilia in this study consist of the following items based upon the last month:

- How many times the child's injection was administered by different persons

- Was work missed due to the child's hemophilia

- Was school missed by the child due to his hemophilia

- Was the caregiver's social/leisure time disrupted due to the child's hemophilia

- Was household/domestic routine disrupted due to the child's hemophilia

Full details of the questionnaire can be found in Appendix A. The data will be summarized descriptively at each visit for the FAS.

7.5.2. Physicians Global Assessment of Response

Investigators record assessments of each patient's response to their assigned rFIXFc regimen using the following 4 point scale:

- Excellent

- Effective

- Partially Effective

- Ineffective

The Investigators' assessments will be summarized by visit for the FAS.

The number and percentage of patients in each response category will be tabulated. Percentages will be based on the number of patients for whom an assessment was provided at the respective visit. This table will also include a cumulative tabulation across all scheduled study visits; patients can be included in this tabulation up to all visits, once for each visit. Percentages for this collection of responses throughout the study will be based on the total number of assessments across all visits. In addition, these assessments will be provided in a data listing.

7.5.3. Surgery

Only data from major surgeries will be summarized for the surgery subgroup of the Full Analysis Set. All data will also be listed and similar listings will be written for data from minor surgeries.

Date of admission for surgery, start/end time for surgery, the surgical procedure performed, blood loss during and post operation, blood products used (including transfusion details for type of transfusion, date administered and amount given), date of discharge from hospital, date of last surgery follow-up and the Investigators'/Surgeons' assessment of response to surgery measurements will be listed for all surgeries. Consumption on the day of surgery, including the number of injections required to maintain hemostasis, along with consumption and the number of injections administered over a 2-week period (Days 1-3, Days 4-14, and Days 1-14) following surgery will also be provided in a listing. The dosing intervals utilized during surgery will be characterized with the minimum and maximum intervals between injections required over this 2-week period.

7.5.3.1. Investigators'/Surgeons' Assessment of Patients' Response to Major Surgery

The Investigators'/Surgeons' assessment (using the 4-point surgery response scale detailed in protocol Appendix D) of the patient's hemostatic response to rFIXFc at 24 hours post-surgery will be summarized categorically and with descriptive statistics for all major surgeries for the FAS. Categorically, the number and percentage of surgeries given each rating will be tabulated. Percentages will be based on the number of surgeries for which a response was provided. Since the response is given as an ordered ordinal scale, the responses have also been given a numeric score (Excellent=1, Good=2, Fair=3, Poor/none=4). A lower average score indicates a better Investigators'/Surgeons' assessment of the patients' response to surgery with rFIXFc. Descriptive statistics will be provided using the numeric value of the 4-point scale.

7.5.3.2. Number of Injections and Dose Required to Maintain Hemostasis During Major Surgery

The number of injections, the mean dose per injection (IU/kg), and the total dose (IU/kg) required to maintain hemostasis during surgery will be summarized for all major surgeries for patients in the FAS. The number of injections per surgery will be summarized categorically (0, 1, 2, 3, 4, >4) and with descriptive statistics. Percentages for the categorical summary will be based on the number of major surgeries. The mean dose per injection and total dose required to maintain hemostasis will be summarized using descriptive statistics. The mean dose per injection will be determined as the average dose across all injections per surgery (including the loading dose); the total dose will be determined as the sum across all injections (including the loading dose) per surgery.

7.5.3.3. Estimated Total Blood Loss and Transfusions Received during Major Surgery

The estimated total blood loss during and post each major surgical procedure will be summarized using descriptive statistics. These data will additionally be summarized for the number of transfusions per surgery (regardless of the type of transfusion), the number of transfusions summed across all surgeries for each type of transfusion, and the number of surgeries requiring each type of transfusion will be summarized categorically for all major surgeries for the FAS. Percentages in the categorical summaries will be based on the number of major surgeries for which the respective data is available.

7.5.3.4. Total rFIXFc Consumption per Major Surgery

Total consumption (IU/kg) per major surgery on the day of surgery, for the first 2 weeks following surgery (Days 1-3, 4-14, and 1-14), and for the overall surgical/rehabilitation period will be summarized using descriptive statistics for all major surgeries for the FAS. The day of surgery refers to the calendar day of the surgery and includes the loading dose given for that surgery. The first 2 weeks following surgery begins the day after surgery and extends for 14 calendar days. The overall surgical/rehabilitation period is defined in Section 5.4.3. Total rFIXFc consumption will be determined as the sum of all doses administered during the referenced time periods.

7.5.3.5. Summary of Bleeds per Major Surgery

The total number of bleeding episodes per major surgery during the surgical/rehabilitation period will be summarized categorically (0, 1, 2, 3, >3) and with descriptive statistics. The total number of surgeries with a bleeding episode with onset during Days 1 to 3, Days 4 to 7, Days 8 to 14, and Days 15 to 28 during the surgical/rehabilitation period will be summarized categorically for all major surgeries for the FAS. A surgery will be included in each interval of time for which there was a bleeding episode that started during that time interval. If a bleeding episode started and resolved and another bleeding episode then started within a given time interval, that surgery will be counted only once in that interval. A bleeding episode that starts in one time interval and continues into the next one will be counted only in the interval in which it started. Percentages for this summary will be based on the number of patients still in the surgical/rehabilitation period during the respective interval of time.

8. PHARMACOKINETIC ANALYSIS

Pharmacokinetic samples are collected during the course of this study at baseline and interim visits. Additionally for patients undergoing ITI, PK samples are collected for the determination of incremental recovery (IR) after a confirmed negative inhibitor in patients undergoing ITI (further details are in Section 7.4.9).

PK activity data will be listed for the main study population and separately for measurements taken during the ITI period.

Activity measurements 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 PK parameters but displayed as "<x" or ">x" in the listings.

IR is calculated using the following formula:

$$\text{IR (IU/dL per IU/kg)} = \frac{(C_{max} \text{ for FIX activity} - \text{Pre-dose FIX activity}) \text{ (IU/dL)}}{\text{Actual dose (IU/kg)}}$$

where:

- C_{max} (maximum concentration) is 30-minute FIX activity post-dose

- FIX activity <0.5 IU/dL was set to 0 IU/dL for calculation of IR.

IR data will be listed and summarized by visit in the FAS for exposure on the episodic and prophylactic treatment regimens.

Repeat Analysis Acceptance Criteria

If the assay value is considered as incongruous or aberrant result, the following calculations and comparisons should be used to accept the repeated result and select the reported value:[2]

- For the repeat analysis to be acceptable, the difference between the original and repeat values should be <40% as calculated below:

$$[(\text{Original} - \text{Repeat})/\text{mean}] \times 100 < 40\%$$

  If this condition is not met, reject the reanalysis and perform repeat analysis in duplicate or report "no result" (NR, e.g., in case of insufficient sample volume).

- If the repeat values are acceptable, the selected value to report will be the mean of the original value and the repeat value.

9. SAFETY ANALYSIS

9.1. General Safety Principles

Safety analyses will be based on the Safety Analysis Set and unless otherwise specified, presented by the treatment regimen groups described in Section 5.1.1.

9.2. Analysis of Primary Endpoint or specified safety endpoints

The primary safety endpoint is the occurrence of inhibitor development as determined from the Nijmegen-modified Bethesda assay. Analysis of the incidence of positive inhibitor formation is detailed in Section 9.4.3.

9.3. Adverse Events

An adverse event (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. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

Bleeding episodes in this patient population are not considered as AEs. Bleeding episodes that meet a serious criterion should be reported as serious adverse events (SAE).

AEs will be classified using the Medical Dictionary for Regulatory Activities (MedDRA) system organ classes and preferred terms. MedDRA version 21.1 will be used in this study. All AEs will be listed.

The incidence of AEs will be summarized by system organ class (SOC) and preferred term (PT). Summaries will be included for all AEs as well as by severity and relationship to treatment. Patient listings will be provided for all AEs, SAEs, related AEs, AEs resulting in discontinuation of study treatment and/or withdrawal from the study, AEs during major surgical/rehabilitation periods, and deaths.

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. 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.

All AE listings will include the onset and resolution study days relative to Study Day 1, which is the date of the first rFIXFc treatment. AEs that are emergent prior to the first rFIXFc treatment, AEs that are emergent during a major surgical/rehabilitation period, and AEs that are emergent on the day of surgery will be flagged. Similarly, AEs that are emergent after inhibitor development will be indicated separately as per the period during which they occurred.

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

9.3.1. Treatment-emergent Adverse Events

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

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 precedes 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.

9.3.2. 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 patients who experienced a TEAE, related TEAE, treatment-emergent SAE, or treatment-emergent related SAE; the number and percentage of patients who discontinued treatment and/or the study due to a TEAE; and the number and percentage of patients who died. This table will be presented by treatment regimen as described in Section 5.1.1.

This summary will also be presented by EPD entry compliance (see Section 6.6.2.3), <80% and >=80%, where >=80% is considered compliant.

9.3.3. Summary of Treatment-Emergent Adverse Events

The overall incidence of TEAEs will be summarized by SOC and preferred term. SOCs and preferred terms within each SOC will be presented alphabetically. For the purpose of

summarization, a patient is counted once in a SOC or preferred term if the patient reported one or more events in that SOC or preferred term. This table will be presented by treatment regimen as described in Section 5.1.1.

This summary will also be presented by EPD entry compliance (see Section 6.6.2.3), <80% and >=80%, where >=80% is considered compliant.

9.3.4. Adverse Events in Descending Order of Incidence

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

9.3.5. Severity of Adverse Events

AEs are classified by the Investigator for severity ("Mild", "Moderate", and "Severe"). An overall summary of TEAEs by SOC, preferred term, and severity will be presented. AEs with a missing severity will be counted as "Severe" in the summary table. A patient will be counted once for each SOC and preferred term based on the greatest severity within that SOC and preferred term, respectively.

9.3.6. 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 by SOC, preferred term, and relationship will be presented. AEs with a missing relationship will be counted as "Related" in the summary table. A patient will be counted once for each SOC and preferred term based on the highest relationship within that SOC and preferred term, respectively.

9.3.7. 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 patient or may require intervention to prevent one of the other outcomes listed above. Events considered medically important, as defined in Section 15.3.2 of the protocol, are also considered to be SAEs.

All SAEs will be listed; treatment-emergent SAEs will be summarized overall by SOC and preferred term.

9.3.8. 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 patient 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.

9.3.9. Deaths on Study

A listing of events leading to death occurring on the study will be provided.

9.3.10. Adverse events of Special Interest

There are no specific AE outputs focusing on events of special interest. Any consideration of these will be based upon medical review of existing outputs.

9.4. Clinical Laboratory Evaluations

All laboratory evaluations will be summarized for the Safety Analysis Set, as described in the rest of this section. Data collected at local laboratories will be excluded from analysis, unless otherwise specified. All laboratory data will be provided in data listings; abnormal values relative to laboratory normal ranges and potentially clinically significant abnormalities will be identified. Laboratory evaluations taken during major surgical/rehabilitation periods will not be included in any summary but will be included in the listings and flagged.

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.

9.4.1. 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, total protein, total bilirubin, gamma glutamyl transferase (GGT), aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase, blood urea nitrogen (BUN), serum creatinine, and glucose.

9.4.1.1. 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. Data from unscheduled visits will be excluded from this analysis. In the event of retests or repeat assessments at the same time point, the last non-missing evaluable measurement will be used for the purpose of analysis.

9.4.1.2. Shifts

Each patient'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 patient. Data collected from unscheduled visits will be included in the determination of the per patient 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 patients with a shift to low (from normal, high, or unknown) and the number of patients with a shift to high (from normal, low, or unknown) will be tabulated; percentages will be based on the number of patients at risk. The number at risk for a shift to low (high) is the number of patients 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 1.

Table 1: **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
ALP	High	Monocytes	Low and High
Total bilirubin	High	Eosinophils	Low and High
GGT	High	Basophils	Low and High
Renal		Red blood cells	Low and High
Blood urea nitrogen	High	Hemoglobin	Low and High
Creatinine	High	Hematocrit	Low and High
Electrolytes		Platelets	Low and High
Sodium	Low and High		
Potassium	Low and High		
Chloride	Low and High		
Other			
Glucose	Low and High		
Total protein	Low and High		

9.4.1.3. Potentially Clinically Significant Laboratory Abnormalities

Abnormal laboratory values will also be evaluated by determining the number and percentage of patients with at least one potentially clinically significant laboratory abnormality over the course of the study that also represents a change 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 Bioverativ's Pharmacovigilance group..

Patients 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 patients with an abnormality. Percentages will be based on the number of patients with at least one post baseline value for the given laboratory test. Threshold levels for potentially clinically significant laboratory abnormalities are provided in Table 2 (hematology) and Table 3 (chemistry). Data collected from unscheduled visits will be included in this analysis.

Table 2: **Threshold Levels for Potentially Clinically Significant Hematology Abnormalities**

	Low	High
Neutrophils	$<1.5 \times 10^9$/L	NA
Eosinophils	NA	$>1.6 \times 10^9$/L
Hemoglobin	<100 g/L	Increase in >20 g/L above ULN
Hematocrit	$<30\%$	$\geq 60\%$
Platelet count	$\leq 75 \times 10^9$/L	$\geq 700 \times 10^9$/L

NA = not applicable

Table 3: **Threshold Levels for Potentially Clinically Significant Chemistry Abnormalities**

	Low	High
Liver		
ALT/SGPT	NA	$>3 \times$ ULN
AST/SGOT	NA	$>3 \times$ ULN
Total bilirubin	NA	$>1.5 \times$ ULN
GGT	NA	$>2.5 \times$ ULN
Renal		
Creatinine	NA	$>1.5 \times$ 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

9.4.2. **Urinalysis**

These assessments were not performed in this study.

9.4.3. Incidence of Inhibitor Development

All the analyses in this section will be presented for the Safety Analysis Set. All analyses of, and derivations based upon, inhibitor test results are performed using the Nijmegen Inhibitor Fc assay and plasma derived (PD) assay.

9.4.3.1. Endpoint Definition

A positive inhibitor occurs where a patient has a value ≥0.6 Bethesda Units (BU/mL) confirmed on re-testing 2-4 weeks later. See Section 5.2.4 for exact definition. 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. Inhibitor test data will be listed for all patients.

9.4.3.2. Primary Analysis

The primary analysis of overall incidence of positive inhibitor formation will be based on all patients in the Safety Analysis Set. Any patient who develops an inhibitor following the initial rFIXFc administration will be included in the numerator. All patients who have received at least 1 dose of rFIXFc will be included in the denominator. An exact 95% confidence interval for the proportion of patients with a positive inhibitor will be calculated using the Clopper-Pearson method for a binomial proportion. PROC FREQ in SAS version 9.4 or higher will be used to produce this confidence interval.

The incidence of positive inhibitor formation will be summarized separately for the types of inhibitor specified in Section 5.2.4, namely:

- Patients with high-titer inhibitors
- Patients with low-titer inhibitors that meet the clinically meaningful criteria
- Patients with low-titer inhibitors that do not meet the clinically meaningful criteria

9.4.3.3. Supporting Analyses

To support the primary analysis results, the following will also be presented, using the primary methodology.

Overall Incidence based upon ED Milestones

The overall incidence of positive inhibitor formation will be presented for all patients who have reached at least 10, 20 and 50 EDs and had at least one inhibitor test performed at or beyond this milestone. For these analyses, any patient who develops an inhibitor following the initial rFIXFc administration will be included in the numerator and denominator. Patients who do not develop an inhibitor but reached the milestone number of EDs will be included in the denominator, i.e.,:

$$\text{Incidence rate} = \frac{\text{Number of patients with an inhibitor}}{\text{Number of patients reaching ED milestone or who have an inhibitor}}$$

Time to Inhibitor Development

The cumulative incidence of inhibitors over time (EDs) will be estimated using the Kaplan-Meier method. For patients who do not have an inhibitor, follow-up time will be censored at the last ED at the time of analysis. This will be presented graphically for high and low titer (CS and NCS) inhibitors and overall, if at least 5 patients develop positive inhibitor.

Additionally a summary of EDs at time of inhibitor development will be provided, again for high and low titer (CS and NCS) inhibitors and overall. This will include Kaplan-Meier estimates of cumulative incidence of inhibitor development at 10, 20 and 50 EDs.

9.4.3.4. Additional Analyses

Patients with low titer inhibitors who remain in the main study may achieve remission without ITI. This is defined as negative inhibitor titers (<0.60 BU/mL) in 2 consecutive determinations 2 – 4 weeks apart. These patients will be listed separately.

9.4.4. Incidence of Anti-FIX Antibodies

The development of anti-rFIXFc ████████████ antibodies will be assessed as the number and percentage of patients negative throughout the study, positive at any time following treatment with rFIXFc, and positive at the final evaluation. Percentages will be based on the number of patients who are antibody negative prior to treatment with rFIXFc and have at least one 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-rFIXFc ████████████ antibodies will be included in this analysis.

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

9.5. Vital Signs

Vital signs include temperature, pulse, systolic and diastolic blood pressure, respiratory rate, height and weight. All vital signs except height and weight were measured prior to and approximately 20 minutes after each dose of rFIXFc. Height and weight were measured prior to dosing. Temperature was measured using the following methods: oral, rectal, tympanic, forehead, and axillary.

Vitas signs will be summarized for the observed values and change from baseline using descriptive statistics for the Safety Analysis Set. Post-baseline temperature measurements taken by a method different from baseline will be excluded from the analysis with the exception of the combination of tympanic and rectal measurements. Evaluations taken during major surgical/rehabilitation periods will not be included in any summary.

A listing of all vital signs will be provided, including from unscheduled visits and during surgical/rehabilitation periods. Vital signs collected during surgical/rehabilitation periods as well as those occurring on the day of surgery will be flagged in this listing.

9.6.   Physical Examination Findings

All physical examination abnormalities with body system will be listed by patient and visit.

10.   CHANGES TO PLANNED ANALYSIS

This SAP is based on Version 3 of the approved study protocol dated 06 August 2018. The major differences in the analysis described in this SAP compared to the protocol are:

- The Full Analysis Set consists of all patients who received at least 1 dose of rFIXFc <u>and were enrolled</u>.

- The protocol mentioned selected analyses may be performed based on a Supporting Analysis Set as appropriate. This analysis set is not defined in the SAP, and all analyses will be based on the analysis populations defined in Section 4.

- The health outcomes questionnaire used in the study is not as specified in the protocol. The analysis described refers to that which was actually used and this can be found in Appendix A.

11. REFERENCES

1. European Medicines Agency. Guideline on the clinical investigation of recombinant and human plasma-derived factor VIII products. EMA/CHMP/BPWP/144533/2009. July 21, 2011.
2. Fluhler et. Al. Repeat Analysis and Incurred Sample Reanalysis: Recommendation for Best Practices and Harmonization from the Global Bioanalysis Consortium Harmonization Team. The AAPS Journal, Vol. 16, No. 6, November 2014.

12. LIST OF TABLES, LISTINGS, AND FIGURES

List of tables

Background/Demography
Summary of disposition by treatment regimen
Summary of enrollment by country and site by treatment regimen
Summary of patients attending key study visits
Summary of patients attending key ITI study visits
Summary of demographics and baseline characteristics by treatment regimen
Summary of medical and surgical history by treatment regimen
Summary of hemophilia history by treatment regimen
Summary of bleeding history in the 3 months prior to study entry by treatment regimen
Summary of risk factors by inhibitor subgroup
Summary of physical examination at screening by treatment regimen
Summary of prior medications and procedures by treatment regimen
Summary of concomitant medications and procedures by treatment regimen
Summary of major protocol deviations by treatment regimen
Exposure/Dosing
Summary of injections and days of exposure to rFIXFc by treatment regimen
Summary of injections and days of exposure to rFIXFc by EPD entry compliance by treatment regimen
Summary of duration of dosing with rFIXFc by treatment regimen
Summary of duration of dosing with rFIXFc by EPD entry compliance by treatment regimen
Summary of prophylactic dose IU/kg
Summary of ITI dose IU/kg
Summary of prophylactic dosing interval
Summary of ITI dosing interval
Summary of annualized rFIXFc consumption (IU/kg) by treatment regimen
Summary of last prescribed prophylactic dose and dosing frequency
Summary of compliance for the treatment of bleeding episodes by treatment regimen
Summary of prophylactic and ITI dose compliance
Summary of prophylactic and ITI dosing interval compliance
Summary of prophylactic and ITI compliance
Summary of EPD entry compliance by treatment regimen
Efficacy
Summary of bleeding episodes by treatment regimen
Summary of annualized bleeding rates by treatment regimen
Summary of annualized bleeding rate by type of bleed and treatment regimen
Summary of annualized bleeding rate by location of bleed and treatment regimen
Summary of annualized bleeding rate by location, type of bleed and treatment regimen
Summary of annualized bleeding rate by history of bleeding (estimated frequency of bleeds in prior 3 months) by treatment regimen

Summary of annualized bleeding rate - patients with no major protocol deviations potentially impacting efficacy by treatment regimen
Summary of patient's assessment of response to rFIXFc injections for the treatment of bleeding episodes by treatment regimen
Summary of patient's assessment of response to rFIXFc injections for the treatment of bleeding episodes by compliance to treat the bleed and treatment regimen
Summary of number of injections required for resolution of a bleeding episode by treatment regimen
Summary of dose (IU/kg) of rFIXFc for resolution of bleeds by treatment regimen
Summary of physician's global assessment of the response for episodic and prophylactic regimens
Summary of physician's global assessment of the response for ITI regimens
Summary of health outcomes for episodic and prophylactic regimens
Summary of incremental recovery (IR) (IU/dL per IU/kg) for episodic and prophylactic regimens
ITI
Summary of ITI response
Surgery
Investigators'/surgeons' assessment of patients' hemostatic response to rFIXFc post major surgery
Number of injections and dose required to maintain hemostasis during major surgery
Estimated total blood loss during major surgery
Total rFIXFc consumption (IU/kg) per major surgery
Summary of number of bleeds after surgery per major surgery
Adverse events
Overall summary of rFIXFc treatment-emergent adverse events by treatment regimen
Overall summary of rFIXFc treatment-emergent adverse events by treatment regimen and EPD entry compliance
Summary of rFIXFc treatment-emergent adverse events by treatment regimen
Summary of rFIXFc treatment-emergent adverse events by treatment regimen and EPD entry compliance
Summary of rFIXFc treatment-emergent adverse events by treatment regimen and preferred term in descending order of incidence
Summary of rFIXFc treatment-emergent serious adverse events by treatment regimen
Summary of rFIXFc treatment-emergent adverse events by severity and treatment regimen
Summary of rFIXFc treatment-emergent adverse events by relationship to treatment and treatment regimen
Summary of severe rFIXFc treatment-emergent adverse events by treatment regimen and preferred term in descending order of incidence
Summary of rFIXFc treatment-emergent adverse events leading to treatment discontinuation and/or study withdrawal by treatment regimen
Routine laboratory
Summary of laboratory results and change from baseline for episodic and prophylactic

regimens: Hematology
Summary of laboratory results and change from baseline for ITI regimen: Hematology
Shifts from baseline to minimum/maximum post-baseline value for laboratory results: Hematology
Summary of shifts from baseline to minimum/maximum post-baseline value for laboratory results: Hematology
Summary of potentially clinically significant laboratory abnormalities: Hematology
Summary of laboratory results and change from baseline for episodic and prophylactic regimens: Blood Chemistry
Summary of laboratory results and change from baseline for ITI regimen: Blood Chemistry
Shifts from baseline to minimum/maximum post-baseline value for laboratory results: Blood Chemistry
Summary of shifts from baseline to minimum/maximum post-baseline value for laboratory results: Blood Chemistry
Summary of potentially clinically significant laboratory abnormalities: Blood Chemistry
Inhibitors
Summary of inhibitor development by Nijmegen-modified Bethesda assay
Summary of time to inhibitor development
Other Safety
Summary of anti-rFIXFc antibodies
Summary of vital sign results and change from baseline for episodic and prophylactic regimens
Summary of vital sign results and change from baseline for ITI regimen

List of listings

Background/demography
Listing of lot numbers for study drug
Listing of protocol versions consented to
Listing of end of study disposition
Listing of demographic and baseline characteristics
Listing of caregiver's demography
Listing of medical and surgical history
Listing of informed consent date and analysis populations
Listing of hemophilia history – diagnosis and diagnostic factors
Listing of Hemophilia history – bleeding history 3 months prior to screening
Listing of risk factors
Listing of prior and concomitant medication taken through the end of study visit
Listing of concomitant medication taken after the end of study visit and prior to follow-up
Listing of maternal concomitant medication taken through the end of study visit
Listing of maternal concomitant medication taken afer the end of study visit and prior to follow-up
Listing of other therapy or concomitant procedures

Listing of major and minor protocol deviations
Exposure/dosing
Listing of all injections and treated bleeding episodes
Listing of injections to treat a bleed
Listing of exposure
Listing of dose and consumption endpoints
Listing of prescribed dose and regimen changes
Listing of compliance endpoints
Efficacy
Listing of the number of bleeding episodes during the efficacy period
Listing of derived bleeding endpoints based on individual bleeding episodes
Listing of derived bleeding and injection endpoints based on patients
Listing of the Investigator's classification of bleeding episodes which differed from the caregiver's classification
Listing of the by-patient summary of the assessment of response to rFIXFc for the treatment of bleeding episodes
Listing of physician's global assessment of the patient's response to his treatment regimen
Listing of health outcomes
Listing of FIX activity levels
Listing of incremental recovery
ITI
Listing of patients on ITI
Surgery
Listing of major surgery information – hospitalization data
Listing of major surgery information – blood loss
Listing of major surgery information – dosing during and for the first 14 days post surgery
Listing of major surgery information – transfusions and surgeon's assessment of hemostatic response to rFIXFc
Listing of injections and bleeding episodes during and for the first 14 days following major surgery
Listing of minor surgery information – hospitalization data
Listing of minor surgery information – blood loss
Listing of minor surgery information – dosing during and on the day of surgery
Listing of minor surgery information – transfusions and surgeon's assessment of hemostatic response to rFIXFc
Adverse events
Listing of adverse events
Listing of serious adverse events
Listing of related adverse events
Listing of adverse events leading to treatment discontinuation and/or study withdrawal
Listing of adverse events during major surgical/rehabilitation periods
Listing of deaths

Routine laboratory
Listing of laboratory normal ranges
Listing of laboratory values: Hematology
Listing of abnormal laboratory values based on the normal range: Hematology
Listing of abnormal laboratory values based on potentially clinically significant abnormalities: Hematology
Listing of laboratory values: Blood Chemistry
Listing of abnormal laboratory values based on the normal range: Blood Chemistry
Listing of abnormal laboratory values based potentially clinically significant abnormalities: Blood Chemistry
Inhibitors
Listing of laboratory values: Inhibitor results
Listing of abnormal laboratory values: Inhibitor results
Listing of inhibitor patients who achieve remission without ITI
Listing of inhibitor patients
Other safety
Listing of laboratory values: Anti-rFIXFc antibodies
Listing of abnormal laboratory values: Anti-rFIXFc antibodies
Listing of vital sign measurements
Listing of abnormal findings from physical examination
Listing of weight

List of figures

Safety
Kaplan-Meier plot of incidence of inhibitor development by exposure days and titer

APPENDIX A. HEALTH OUTCOMES QUESTIONNAIRE

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