Bioverativ	Statistical Analysis Plan	Final v1.0

997HA306

STATISTICAL ANALYSIS PLAN

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Product Studied: Recombinant Factor VIII Fc Fusion Protein (rFVIIIFc)

Protocol Number(s): 997HA306

An Open-Label, Multicenter Evaluation of the Safety and Efficacy of Recombinant Coagulation Factor VIII Fc Fusion Protein (rFVIIIFc; BIIB031) in the Prevention and Treatment of Bleeding in Previously Untreated Patients with Severe Hemophilia A

Date of Protocol: 12 February 2018 (Version 6)

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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
FVIII	Coagulation Factor VIII
FU	Follow-up
g	Gram
GGT	Gamma Glutamyl Transferase
HIV	Human Immunodeficiency Virus
IA	Interim Analysis

IR	Incremental Recovery
ITI	Immune Tolerance Induction
IU	International Unit
IXRS	Interactive Voice/Web Response System
kg	Kilogram
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
rFVIIIFc	Recombinant Coagulation Factor VIII 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
$t_{½}$	Half-life
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 997HA306 is a Phase 3, open label, single arm, multicenter study designed to evaluate the safety and efficacy of recombinant coagulation factor VIII Fc fusion protein (rFVIIIFc; BIIB031) in the prevention and treatment of bleeding in previously untreated male patients ages < 6 years with severe hemophilia A, in accordance with the EMA CHMP guideline on the clinical investigation of recombinant and human plasma-derived factor VIII products.[1]

This statistical analysis plan (SAP) will describe:

- An interim analysis (IA) of 997HA306 study data when at least 50 patients have reached at least 50 exposure days (EDs) with rFVIIIFc; an exposure day is defined in Section 5.1.2.4.
- A final analysis of 997HA306 study data when at least 90 patients have reached at least 50 EDs with rFVIIIFc.

This SAP is based on Version 6 of the approved study protocol dated 12 February 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(s)

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

2.1.2. Secondary Objectives

The secondary objectives of this study are:

- To evaluate the efficacy of rFVIIIFc in the prevention and treatment of bleeding episodes in PUPs.
- To evaluate rFVIIIFc consumption for the prevention and treatment of bleeding episodes in PUPs.
- To describe experience with the use of rFVIIIFc for immune tolerance induction (ITI) in patients with inhibitors.

2.1.3. Exploratory Objectives

The exploratory objectives are:

- To evaluate the effect of rFVIIIFc based on patient-reported outcomes (PROs) and health resource utilization.

- To assess the efficacy of rFVIIIFc for perioperative management.

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 rFVIIIFc for bleeding episodes, using the 4-point bleeding response scale.
- The total number of EDs per patient per year
- Total annualized rFVIIIFc consumption per patient for the prevention and treatment of bleeding episodes.
- The number of injections and dose per injection of rFVIIIFc required to resolve a bleeding episode.
- rFVIIIFc incremental recovery (IR).
- Response to ITI with rFVIIIFc (complete success, partial success, failure, early withdrawal).

2.2.3. Exploratory Endpoints

The exploratory endpoints include, but are not limited to:

- Health Outcomes
- Investigator/Surgeon's Assessment of Response

2.2.4. Pharmacokinetic Endpoints

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

2.2.5. Pharmacodynamic Endpoints

There are no pharmacodynamic endpoints 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 rFVIIIFc in PUPs with severe hemophilia A 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 1 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 ITI regimen only for patients who develop inhibitors. After exposure to rFVIIIFc, any patient who develops a positive high-titer inhibitor or a positive low-titer inhibitor (both defined in Section 5.1.2.4) with poorly controlled bleeding despite increased rFVIIIFc doses or who requires the use of bypassing agents to treat bleeding, may be eligible for the ITI regimen.

Approximately 105 patients are planned to be dosed with rFVIIIFc to achieve at least 90 patients with at least 50 EDs by the end of the study. One ED is defined as a 24-hour period in which a patient receives 1 or more doses of rFVIIIFc, with the time of the first injection of rFVIIIFc defined as the start of the ED. The study will end after at least 90 patients have reached at least 50 EDs with rFVIIIFc.

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 rFVIIIFc.

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

The episodic (on-demand) regimen is optional in this study, and, if implemented, must precede initiation of the prophylactic treatment regimen. Dosing and duration of episodic treatment is determined by the Investigator. 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, which is the target population in this study, 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 dose for initiation of prophylaxis may be chosen by the Investigator within the range of 25 to 80 IU/kg. Treatment continues until the patient reaches at least 50 EDs to study drug, or completes follow-up of an ITI regimen (if applicable), or the end of study is declared by Bioverativ.

3.1.2.3. Immune Tolerance Induction (ITI) Treatment Regimen

After exposure to rFVIIIFc, any patient who develops a positive high-titer inhibitor or a positive low-titer inhibitor (both defined in Section 5.1.2.4) with poorly controlled bleeding, is eligible to undergo an ITI regimen with rFVIIIFc. The ITI treatment regimen consists of single injections of rFVIIIFc 200 IU/kg/day, consistent with current ITI guidelines.[2] Duration of ITI treatment is up to 33 months, followed by a tapering off regimen of at least 3 months (12 weeks). Separate consent is required before starting an ITI treatment regimen.

3.1.3. Procedures for Discontinuing Treatment and Removal of Patients from the Study

The parent/legal guardian may withdraw the patient from the study, or the patient may withdraw from the study, at will at any time. A patient must discontinue study treatment and be withdrawn from the study for any of the following reasons:

- The patient is found to have a factor VIII (FVIII) activity ≥1% or a positive inhibitor based on central laboratory results obtained during the Screening Period.
- The patient develops a positive inhibitor following enrollment and is eligible for ITI AND opts not to undergo or continue ITI.
- A patient who is in the tapering period (or the subsequent follow-up monitoring period) of the ITI treatment regimen and develops inhibitors (that is, had a relapse).
- The patient develops a ≥Grade 2 allergic drug reaction in association with the administration of rFVIIIFc, as defined by the Recommendations for Grading of Acute and Subacute Toxic Effects on the World Health Organization (WHO) scale:[3]
    - Grade 2: bronchospasm; no parenteral therapy needed
    - Grade 3: bronchospasm; parenteral therapy required
    - Grade 4: anaphylaxis
- The patient uses FVIII products other than rFVIIIFc (exception allowed for 1 emergency or accidental use).
- The patient receives concomitant immunomodulation.
- The patient develops any condition that precludes him from complying with the study procedures.

- The patient experiences a medical emergency that necessitates discontinuation of treatment.
- It is not in the patient's best interest to continue with the study treatment, in the judgment of the Investigator.
- The parent/legal guardian decides to withdraw the patient from the study.

At the discretion of the Investigator, a patient may be withdrawn due to noncompliance.

The reason for the patient's withdrawal from the study must be recorded in the patient's eCRF.

For any patient who is not responding to treatment with rFVIIIFc, as determined by the Investigator, a decision will be made with the Bioverativ Medical Monitor whether to continue the patient in the study.

3.1.4. End of Study

End of the study (EOS) will occur after at least 90 patients have reached at least 50 EDs with rFVIIIFc.

3.1.5. Dose Adjustments

All bleeding episodes are to be treated with study drug. The dose to treat the bleeding episode will be based on the patient's clinical condition, known PK information, type and severity of the bleeding episode, and input from the Medical Monitor, if necessary.

3.1.5.1. Episodic Treatment Dose Adjustment

The Investigator has the option to treat the patient episodically, starting after the confirmation of eligibility and lasting until a prophylactic treatment regimen is initiated. Dosing will be determined by the Investigator using the guidelines in Appendix A of the approved study protocol.

3.1.5.2. Prophylactic Treatment Dose Adjustment

The dose for initiation of prophylaxis may be chosen by the Investigator within the range of 25 to 80 IU/kg. The dose can be adjusted based on the patient's response to dosing in the range of 25 to 65 IU/kg at 3- to 5-day intervals. Adjustments to the dose and dosing interval can be made based upon available IR data, subsequent FVIII activity levels, level of physical activity, and bleeding pattern, in accordance with local standards of care for a prophylactic treatment regimen.

3.1.5.3. Immune Tolerance Induction (ITI) Dose Adjustment

An ITI regimen comprises of high daily doses of replacement factor. Therefore regimen in this study approximates the high-dose treatment arm of the International ITI Study protocol, and utilizes single injections of rFVIIIFc of 200 IU/kg/day. After a maximum of 33 months of ITI, the administered dose will be tapered off as follows:

[redacted]

[redacted]

After this tapering period, the patient reverts to a prophylactic treatment regimen for the relapse monitoring period. See Section 7.4.9 for further details.

3.1.6. 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 is 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 105 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 rFVIIIFc in this population of primarily very young children, approximately 105 patients will be dosed with rFVIIIFc to achieve at least 90 patients with at least 50 EDs by the completion of the study.

3.4. Randomisation and Blinding

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

3.5. Interim Analysis

There will be one interim analysis, performed when the study milestone of at least 50 patients with 50 EDs is reached and the 50 ED inhibitor tests for all patients who reach this milestone have been performed and have present and valid results. Except where indicated, the analyses described in this plan will be performed for both the interim and final analyses.

4. ANALYSIS POPULATIONS

By definition, the patients included in these population sets will differ between the interim and final analyses.

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 rFVIIIFc 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 rFVIIIFc. 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 rFVIIIFc. All analyses and summaries of efficacy and exploratory endpoints will be based on the FAS, unless otherwise specified in this SAP.

4.4. ITI Analysis Set

The ITI Analysis Set is defined as all patients who consent to and initiate the ITI sub-study (see Section 3.1.2.3). All analyses and listings of data from the ITI sub-study will be presented for this population.

5. DEFINITIONS AND DATA HANDLING

Study 997HA306 is being conducted under the sponsorship of Bioverativ Therapeutics Inc. Data management is being performed under contract with Quintiles 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 6 of the approved study protocol dated 12 February 2018 and details the analyses to be performed and summaries to be produced for the interim and final analyses for the Clinical Study Report(s) (CSRs).

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.

Data will be summarized using standard summary statistics for continuous and categorical data, as appropriate (additional information is provided in Section 5.3).

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 ad safety data include an overall/total column and those for efficacy and outcome data do not. Any exceptions to this are specified in the relevant section.

5.1.1.1. General

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 5.2 and 5.4.

5.1.1.2. Inhibitor Subgroups

Selected tables will further be presented by the following groups:

- Patients in the inhibitor subgroup (see Section 5.1.2.5)
- Patients not in the inhibitor subgroup

For longitudinal data, the safety or efficacy periods included for these groups is the entire period, again as described in Section 5.4.

Patients in the inhibitor subgroup will be further split by the sub-classification of inhibitor as described in Section 5.1.2.5, namely:

- Patients with high-titer inhibitors
- Patients with low-titer inhibitors that meet the clinically meaningful criteria as defined in Section 5.1.2.5
- Patients with low-titer inhibitors that do not meet the clinically meaningful criteria

For this presentation, the analysis of longitudinal data will be presented for the entire safety or efficacy periods, dichotomized as described in Section 5.4.7, i.e.:

- From start of the relevant period up to the date of the positive inhibitor (all patients in the inhibitor subgroup combined)
- From date of positive inhibitor to the end of the relevant period

The definition of a positive inhibitor and the date of onset are described in Section 5.1.2.4.

5.1.2. Definitions

5.1.2.1. Description of 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 rFVIIIFc. 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.

5.1.2.2. Visit Windows

Screening Visit

Screening assessments must be completed within a total of 8 weeks from the start of screening activities (with the exception of informed consent, which may have occurred earlier). If more than 8 weeks have elapsed, and the patient is not enrolled in the study, then the Nijmegen inhibitor and FVIII antibody assessments must be repeated. Other screening assessments that are not completed must be completed within an additional 8 weeks, except for the collection of the genotyping sample. If necessary, a genotyping sample could be sent to the central laboratory at a subsequent interim visit.

Baseline Incremental Recovery Visit

Baseline IR Visit activities are performed as soon as practicable once all eligibility criteria were met and the patient is enrolled. This visit may be conducted along with other baseline

assessments on the same day as screening, once the patient has been enrolled, or as part of a separate baseline IR visit, as long as the patient has not yet had more than 3 doses of rFVIIIFc. Samples for IR calculations are taken when the patient is in a non-bleeding state. Baseline IR requires a washout from rFVIIIFc of at least 24 hours prior to the predose sample collection.

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 ED (±1 ED), 10 ED (10-15 ED), 20 ED (20-25 ED) and 50 ED (50-55 ED).

ITI Visits

After a patient on episodic or prophylactic treatment is confirmed as having high- or low-titer inhibitors with poorly controlled bleeding, the patient participates in ITI visits. Pre-ITI assessment is on ITI Day 0. The first interim ITI visit is ITI Week 2 (± 3 days). Subsequent ITI interim visits are every 4 weeks until a negative titer is confirmed. After a negative titer is confirmed, interim visits are every 4 weeks until ITI Complete Success or a maximum of 33 months of treatment (see Section 7.4.9).

Patients with a confirmed negative inhibitor titer and confirmed IR ≥66% of expected who have not yet achieved the criteria for ITI complete success, will undergo PK evaluation for t½ every 12 weeks.

Post Immune Tolerance Success Visits

Patients who fulfill the criteria for ITI complete success or 33 months of ITI treatment then transition to a "tapering" regimen over a minimum period of 12 weeks with the aim of starting a prophylactic rFVIIIFc regimen, and are monitored for relapse for up to 9 months.

Tapering visits are every 4 weeks (± 1 week) within a 12-week period.

Follow-up monitoring for relapse visits are every 12 weeks (± 2 weeks) within a 9 month period.

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 FVIII activity and Nijmegen-modified Bethesda assay. For minor surgery, the Investigator will be in contact with the patient's parent/caregiver to determine when the patient may return to the regular prophylactic treatment 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 prophylactic treatment regimen. This visit is not required if the return to the regular prophylactic treatment regimen occurs at the Postoperative Visit. If the patient is withdrawn from the study, then the patient completes the ET/EOT Visit assessments at least 2 weeks after surgery.

End-of-Treatment Visit

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

- Any individual patient who completes at least 50 EDs of rFVIIIFc and is not on an ITI regimen has completed treatment.
- A patient undergoing ITI with rFVIIIFc has completed treatment if either of the following occurs:
    - The patient achieves complete ITI success and completes the tapering and monitoring periods.
    - The patient completes 33 months on an ITI regimen without achieving complete ITI success (that is, ITI failure or partial ITI success).
- Individual patients may also be required to end treatment because one of the following has occurred:
    - The patient meets the criteria for early withdrawal.
    - Study stopping rules are met.
    - EOS is reached.

Final Safety Follow-Up Visit

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

5.1.2.3. Baseline

Unless specified otherwise, for the purpose of analyses involving change from baseline during treatment with rFVIIIFc, 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 rFVIIIFc.

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

5.1.2.4. Study-Specific Definitions

Exposure Day

One ED is defined as a 24-hour period in which a patient receives 1 or more doses of rFVIIIFc, with the time of the first injection of rFVIIIFc 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 bleeding and ends no more than 72 hours after the last injection to treat the bleeding, 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 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 records a bleeding episode even when there is a known or believed reason for the bleeding. 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. The Investigator considers whether events resulting in a traumatic bleeding episode qualify as AEs and reports as such.

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 at least 2 weeks after the date when the original sample was drawn. Both tests must be performed by the central laboratory using the Nijmegen-modified Bethesda assay and 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 third separate sample, drawn at least 2 weeks after 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.

In either case, the date of the inhibitor is the date of the sample with the first positive test result.

If, as per the algorithm above, a patient is initially classified as having a low titer inhibitor which subsequently becomes high titer using the same rules, this patient may be re-classified as follows:

- If the patient's inhibitor becomes high titer without a significant increase in dose, defined as a dose that more than doubles between the time of development of the low titer and high titer inhibitors, then the patient should be considered high titer for the entire inhibitor period
- If the patient's inhibitor becomes high titer after a significant increase in dose, defined as a dose that more than doubles, or after the patient commences ITI, then the patient should be considered low titer for the entire inhibitor period

All analysis of, and derivations based upon, inhibitor test results are performed using the Nijmegen Inhibitor Fc assay test.

5.1.2.5. 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 Subgroup

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

1. Patients with high-titer inhibitors, defined as in Section 5.1.2.4
2. Patients with low-titer inhibitors, defined as Section 5.1.2.4, 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 just prior to the interim or 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 sub-study
- 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 (rFVIIIFc) regimen

Patients who undergo ITI will be part of the ITI Analysis Set (see Section 4.4). By definition, all high-titer inhibitors are clinically meaningful, as patients with high-titer inhibitors must either enter the ITI sub-study or withdraw.

5.1.2.6. End of Study

The end of the study (EOS) will occur after at least 90 patients have reached at least 50 EDs with rFVIIIFc. Once this milestone has been achieved, all ongoing study patients will return to the study center for their final visits.

5.1.3. Pooling Sites for Analysis

All sites will be pooled and reported together for analysis.

5.1.4. 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 the ITI subset, 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.

5.2. 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.

5.2.1. 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 rFVIIIFc 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

5.2.2. 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 rFVIIIFc 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.

5.2.3. 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 the 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 the 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 the 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.
- From a ITI regimen to a prophylactic regimen (tapering): If there is no ITI dose on the day of treatment regimen change recorded in the eCRF, the prophylactic regimen starts at 00:01 on the day of treatment regimen change, and the ITI regimen ends at 23:59 on the day prior to the day of treatment regimen change. If there is an ITI dose on the day of treatment regimen change, the prophylactic regimen starts 1 minute after that dose, and the ITI regimen ends on the date and time of that dose.

5.2.4. 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.

5.3. Data Summaries

5.3.1. 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; for data collected to 1 decimal place, the mean and median will be presented to 2 decimal places and the SD to 3 decimal places; and so forth. 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).

5.3.2. Categorical Variables

Categorical variables (e.g., ITI response) 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 rFVIIIFc.

5.3.3. Event Time Variables

The only such variable being analysed in this study is the time to inhibitor (see Section 5.1.2.4 for complete definition). The cumulative incidence of these inhibitors over time (EDs) will be estimated using the Kaplan-Meier method and presented graphically.

5.4. 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 rFVIIIFc.

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 5.2.4 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 (depending on whether there is a treatment regimen change during the surgical/rehabilitation period) 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 (depending on whether there is a treatment regimen change during the surgical/rehabilitation period) 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 a 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 rFVIIIFc 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 rFVIIIFc given for the surgery (i.e., the pre-surgery dose) up to 1 minute before the first regular prophylactic dose after the last day of 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 was a prophylactic dose the day before surgery, this prophylactic dose 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 prophylactic dose on or after the last date among the dates for discharge from the hospital, post-operative visit 1, post-operative visit 2, and the end of rehabilitation.
- If all of the dates mentioned above are missing, then select the first prophylactic dose after the date/time for the end of surgery. If the surgery time was not recorded then select the surgery date and impute 23:59 for the time. If the end date of the surgery is missing then select the start date of the surgery and impute 23:59 for the time.

- If there are no prophylactic doses following the latter of the 5 dates mentioned above, then select the latter of the dates and impute 23:59 for the time if otherwise there is no time associated with the given date (e.g., the patient completed the surgical/rehabilitation period but received no further prophylactic doses).
- 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.
- 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.

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

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

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

5.4.4. Safety Period

The overall safety period is defined as beginning at the first dose of study medication rFVIIIFc. 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), 7 to 14 days after the last dose of rFVIIIFc. 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 5.2 except that the end of the patient's last treatment regimen is the end of their safety period.

5.4.5. Pharmacokinetic Period

There is no defined PK period in this study.

5.4.6. Follow-up Period

The follow-up period is defined as the period 7 to 14 days after the last dose of rFVIIIFc.

5.4.7. Inhibitor Period

For patients who develop inhibitors, safety and efficacy data analysis will be dichotomized into periods before and after this event. The date of the inhibitor, that is, the date of the first sample with a positive test result (subsequently confirmed, see Section 5.1.2.4) will be leveraged for this purpose. The start and end of the inhibitor period are the start and end the relevant period, as defined in Sections 5.4.2 and Section 5.4.4.

5.4.8. 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.

5.5. 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 only allow 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, but 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 5.1.1.1.

6.1. Disposition of Patients

Patient disposition will be summarized for the All-Enrolled Analysis Set. This table will present the number of patients in the Full Analysis Set (FAS), the number of patients with an efficacy period, the number of patients in the Safety Analysis Set and the number of patients in the Surgery Subgroup. The number and percentage of patients who completed/discontinued the study, including the primary reason for those who discontinued, will be tabulated. This table will be presented by treatment regimen and for the inhibitor subgroups, as described in Sections 5.1.1.1 and 5.1.1.2 respectively.

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. This analysis will also be performed for the ITI Analysis Set, 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 France, Germany, Ireland, Italy, the Netherlands, Poland, Spain, Sweden, and the United Kingdom. North America includes Canada and the United States. Other countries include Australia, Brazil, 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 5. This table will be presented by treatment regimen and for the inhibitor subgroups, as described in Sections 5.1.1.1 and 5.1.1.2 respectively.

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 FVIII activity values will be summarized categorically (<1%, ≥1%). Categorical summaries will also be provided for FVIII 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 FVIII 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 5.1.2.5:

- 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
- FVIII 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
    - Medium risk – splicing variants or inversions of intron 1 and intron 22
    - Low risk - small deletions/insertions or missense variants
    - 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 rFVIIIFc 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 rFVIIIFc. Prior medications are all drugs and substances taken before the first rFVIIIFc dose was received. Concomitant medications are those administered during or after the first injection of rFVIIIFc while on study, or administered prior to the first administration of rFVIIIFc and ongoing at the start of rFVIIIFc administration.

Prior and concomitant medications will be characterized based on the onset and resolution dates relative to the date and time of the first dose of rFVIIIFc. Medications reported for a 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 rFVIIIFc and was ongoing during and/or after the first dose of rFVIIIFc will be classified as both prior and concomitant.
- Medications with a start date after the follow-up visit will not be considered concomitant and will not be included in the summary tables.
- For partial dates, if a concomitant medication start day is missing then the medication will be assumed to be both a prior and a concomitant medication unless the start month and/or year or medication stop date can be used to determine if a medication is concomitant or prior, as follows:

- If the concomitant medication start day is missing, but the month and year are before the start month and year of the first dose of rFVIIIFc and the concomitant medication stop date is before the start day of the first dose of rFVIIIFc, then the medication will be classed as prior only.
- If the day of the start date is missing and the month and year are after the month and year of the first dose of rFVIIIFc then the medication will be classed as concomitant only.
- If the month of the start date is missing and the year is before the start year of the first dose of rFVIIIFc and the stop date is before the start date of the first dose of rFVIIIFc, then the medication will be classed as prior only.

In this study, for patients who receive breast milk, maternal concomitant medications are also be 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 a separate table, 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 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 were all 25 IU/kg at the Baseline IR Visit, 50 IU/kg during the ITI regimen for IR and t½ assessments, and were calculated using the actual potency of the vial (between 80 to 125% of nominal strength) and used 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:

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

PK doses were not used for the purpose of preventing or treating bleeding and therefore the total annualized rFVIIIFc consumption will exclude the IU/kg amount that was 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 rFVIIIFc

For any patient, the total number of days of exposure to rFVIIIFc will be accumulated from the time of their first on-study injection of rFVIIIFc. An ED is a 24-hour period in which one or more rFVIIIFc injections are given. The 24-hour window starts from the first injection on study and then for subsequent injections, it starts from an injection taken after/outside of a previously identified ED.

The total number of EDs on rFVIIIFc 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 or other) using descriptive statistics for the Safety Analysis Set.

These tables will be presented by treatment regimen and for the inhibitor subgroups, as described in Sections 5.1.1.1 and 5.1.1.2 respectively.

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 rFVIIIFc Dosing

The duration of rFVIIIFc dosing will begin from the first rFVIIIFc dose (episodic or prophylactic) and end with the last rFVIIIFc dose, regardless of the reason for the last dose (e.g.,

prophylaxis, to treat a bleeding episode, surgical). Duration will be calculated as the date of the last dose minus the date of the first dose +1. Any interruptions to dosing will 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 rFVIIIFc 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 and for the inhibitor subgroups, as described in Sections 5.1.1.1 and 5.1.1.2 respectively.

Duration of rFVIIIFc 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 categorically for the prophylactic and ITI treatment periods.

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

The average weekly (daily for ITI) 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 PRx and the sum of interval durations (PRx+1 minus PRx) will be determined across all evaluable intervals of PRx to PRx+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.

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

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

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

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 rFVIIIFc consumption (IU/kg) will be calculated for each patient using the following formula:

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

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

Total annualized rFVIIIFc 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 5.1.2.4. 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 24 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 day (+/- 24 hours) in order to be compliant, or +/- 12 hours for ITI regimens, as these are daily dosing or more frequent.

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 rFVIIIFc.

$$\text{Dose interval compliance rate} = \frac{\text{Number of doses taken within +/- 24 hours (+/- 12 hours for ITI regimens) of prescribed day/time}}{\text{Total number of intervals}} \times 100$$

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 ≥80% 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 ±24 hours (±12 hours for ITI) 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 5.1.1.1.

Additionally, the general efficacy and surgical/rehabilitation periods are defined in Section 5.4. Data on bleeding and rFVIIIFc 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 5.1.2.4

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 and for the inhibitor subgroups, as described in Sections 5.1.1.1 and 5.1.1.2 respectively.

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:

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

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 and for the inhibitor subgroups, as described in Sections 5.1.1.1 and 5.1.1.2 respectively.

This analysis will also be presented by the following subgroups:

- 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 and for the inhibitor subgroups, as described in Sections 5.1.1.1 and 5.1.1.2 respectively.

7.4.5. Assessment of Response to Treatment with rFVIIIFc 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 rFVIIIFc 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 rFVIIIFc 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 patient 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 rFVIIIFc for each patient will be summarized. This analysis is described in Section 6.6.1.1.

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

Total annualized rFVIIIFc 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 rFVIIIFc consumption derivation.

These tables will be presented by treatment regimen and for the inhibitor subgroups, as described in Sections 5.1.1.1 and 5.1.1.2 respectively.

7.4.8. Number of Injections and Dose per Injection of rFVIIIFc 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 and for the inhibitor subgroups, as described in Sections 5.1.1.1 and 5.1.1.2 respectively.

7.4.9. Response to Immune Tolerance Induction (ITI)

The ITI Analysis Set will be analyzed for response to the treatment regimen. Possible treatment responses are:

Complete Success

All of the following criteria are met:

1. Negative inhibitor titers in 2 consecutive determinations at least 28 days apart
2. IR ≥66% of baseline in 2 consecutive determinations at least 28 days apart
3. $t_{½}$ ≥6 hours

Partial Success

The determination of partial success will be made only for patients who have completed 33 months of ITI but who do not fulfill the criteria for complete success. To achieve partial success, the following criteria must be met after patients have completed 33 months of ITI:

- Negative inhibitor titers on 2 consecutive determinations at least 28 days apart AND
- Either of the following (but not both):
  - IR ≥66% of baseline in 2 consecutive determinations at least 28 days apart, or
  - $t_{½}$ ≥6 hours

[redacted]

Failure:

ITI failure is defined as the inability to meet criteria for Complete Success or Partial Success after 33 months on ITI.

Early Withdrawal/ITI Ongoing:

Patients may withdraw from the study during the ITI period before reaching 33 months or complete or partial success. In addition, any patients still in the ITI sub-study at the time of EoS or interim analysis will be included in this category.

Response categories of complete success, partial success, failure, and early withdrawal will be presented overall for the ITI Analysis Set, and separately for the inhibitor subgroups specified in Section 5.1.2.5, namely:

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

Patients fulfilling the criteria for complete success will transition to a "tapering" regimen over a minimum period of 12 weeks with the aim of starting a prophylactic rFVIIIFc regimen, as described in Section 10.2.7.5 of the protocol, and will be further monitored for relapse for up to 9 months as described in Section 10.2.7.6 of the protocol.

During this period, the monitoring for relapse is via blood samples processed by the central laboratory using the Nijmegen-modified Bethesda assay for inhibitor detection, as well as IR assessments. The inhibitor titer and IR will be measured every 3 months during the follow up period. rFVIIIFc $t_{½}$ assessments will be performed 12 months after ITI success. If any of these tests reverse previously met criteria, at any time between the start of tapering through the beginning of prophylaxis, the tests must be repeated within 2 to 4 weeks to confirm relapse.

Relapse is defined as any of the following, occurring within 12 months following complete ITI success:

- A positive inhibitor (≥0.6 BU/mL using the Nijmegen assay) that is confirmed by a second test result of ≥0.60 BU/mL from a separate sample, drawn at least 2 weeks following the date that the original sample was drawn.
- [redacted]
- t½ <6 hours.

The incidence of relapse during both the tapering and formal relapse monitoring period, in patients who are complete successes, will also be part of the summary.

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, IR, and $t_{½}$ 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 infusion/injection was administered by different persons/in different locations
- Whether the parent/caregiver missed any work due to the child's hemophilia
- Whether the child missed any school due to their
- Whether the parent/caregivers social/leisure time became disrupted due to the child's hemophilia

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

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

7.5.2. Physicians Global Assessment of Response

Investigators recorded assessments of each patient's response to their assigned rFVIIIFc 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 Appendix 2) of the patient's hemostatic response to rFVIIIFc 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 rFVIIIFc. 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 rFVIIIFc 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 rFVIIIFc 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 were collected during the course of this study at baseline and before and during surgery. Additionally for patients undergoing ITI, PK samples were collected for the determination of IR and $t_{½}$ as applicable (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.

PK samples for Incremental recovery (IR) assessments are collected at the Baseline IR Visit, all interim visits and after a confirmed negative inhibitor in patients undergoing ITI.

IR is calculated using the following formula:

$$\text{IR (IU/dL per IU/kg)} = \frac{\text{(Cmax for FVIII activity – Pre-dose FVIII activity) (IU/dL)}}{\text{Actual dose (IU/kg)}}$$

where:

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

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 5.1.1.1 .

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 patient administered a pharmaceutical product and 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). All bleeding episodes after the Baseline Visit will be captured in the EPD that the patient's parents/caregivers will be maintaining throughout the study period.

AEs will be classified using the Medical Dictionary for Regulatory Activities (MedDRA) system organ classes and preferred terms. MedDRA version 20.0 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, AEs resulting in discontinuation of study treatment and/or from the study, 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 adverse event listings will include the onset and resolution study days relative to Study Day 1, which is the date of the first rFVIIIFc treatment. AEs that are emergent prior to the first rFVIIIFc 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 rFVIIIFc 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 and for the inhibitor subgroups, as described in Sections 5.1.1.1 and 5.1.1.2 respectively.

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 system organ class (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 and for the inhibitor subgroups, as described in Sections 5.1.1.1 and 5.1.1.2 respectively.

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 15.1.2 of the protocol, are also considered to be SAEs.

All SAEs will be listed; treatment-emergent SAEs will be summarized overall by system organ class 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
Total bilirubin	High	Monocytes	Low and High
GGT	High	Eosinophils	Low and High
Renal		Basophils	Low and High
Blood urea nitrogen	High	Red blood cells	Low and High
Creatinine	High	Hemoglobin	Low and High
Electrolytes		Hematocrit	Low and High
Sodium	Low and High	Platelets	Low and High
Potassium	Low and High		
Chloride	Low and High		
Other			
Glucose	Low and High		
Total protein	Low and High		

9.4.1.3. 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 worsening from baseline. The potentially clinically significant

levels are based on Grade 2 or higher thresholds from the Common Toxicity Criteria for Adverse Events (CTCAE v 4.02 2009) where possible, or were defined by 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%	≥60%
Platelet count	≤75 x 10^9/L	≥700 × 10^9/L

NA = not applicable

Table 3: Threshold Levels for Potentially Clinically Significant Chemistry Abnormalities

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

NA = not applicable, ULN = upper limit of normal

9.4.2. 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 test. In the event of a positive test, a second, plasma derived (PD) test will be performed. These PD test results will be listed only.

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 at least 2 weeks later. See Section 5.1.2.4 for exact definition. Both tests must be performed by the central laboratory. 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 and separately for patients with positive inhibitors.

9.4.3.2. Primary Analysis

The primary analysis of overall incidence of positive inhibitor formation, is based on all patients who have reached at least 10 EDs and had at least one inhibitor test performed at or beyond this milestone. Additionally, any patient who develops an inhibitor following the initial rFVIIIFc

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.,:

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

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.

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 1, 20 and 50 EDs and had at least one inhibitor test performed at or beyond this milestone.

Incidence by Titer

The incidence of positive inhibitor formation will be analysed separately for the types of inhibitor specified in Sections 5.1.2.4 and5.1.2.5, namely:

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

These analyses will all be based upon all patients with at least 1, 10, 20 and 50 EDs.

Time to Inhibitor Development

The cumulative incidence of inhibitors over time (EDs) will be estimated using the Kaplan-Meier method. This will be presented graphically for high and low titer (CS and NCS) inhibitors, as defined in Sections 5.1.2.4 and5.1.2.5, as well as overall CS and overall. For patients who do not have an inhibitor, follow-up time will be censored at the last ED at the time of analysis.

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

Incidence by Peak Titer

The incidence rate of high and low titer inhibitor formation will be estimated and presented for peak titers, defined as the highest titer level detected during testing, dichotomized by:

- High titer, where peak titer ≥5.00 BU/mL
- Low titer, where peak titer ≥0.60 and <5.00 BU/mL.

These analyses will be based upon all patients with at least 1, 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 at least 28 days apart. These patients will be listed separately.

9.4.4. Incidence of Anti-FVIII Antibodies

The development of anti-rFVIIIFc [redacted] antibodies will be assessed as the number and percentage of patients negative throughout the study, at each study visit, at any time following treatment with rFVIIIFc, and at the final evaluation. Percentages will be based on the number of patients who are antibody negative prior to treatment with rFVIIIFc 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-rFVIIIFc [redacted] antibodies will be included in this analysis.

In addition to a listing of all anti-rFVIIIFc [redacted] 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, pulse, temperature, height and weight. All vital signs except height and weight were measured prior to and approximately 20 minutes after each dose of rFVIIIFc. 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. Temperature measurements not taken by the same method pre and post dose 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 6 of the approved study protocol dated 12 February 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 rFVIIIFc and were enrolled.
- An ITI Analysis Set and period was defined for the analysis of immune tolerance induction response data.
- 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

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[redacted]

[redacted]

Bioverativ

To: TMF – 997HA306

Re: Quality Memo to Regarding SAP for 997HA306

This memo is to document that V1.0 of this Statistical Analysis Plan is March 30, 2018 and the original date on the cover sheet which was approved was erroneously recorded as April 30, 2018.
This date has been corrected, initialed and dated by the author on the final version of the document which is filed in this TMF.

The SAP was effective upon approval on 03 Apr 2018.

Quality Memo Completed By:	[redacted]
Signature: [redacted]	Date: 17 APR 2018