# Statistical Analysis Plan
# NCT03103542

# STATISTICAL ANALYSIS PLAN

**Sobi.Elocta-003**

**A Non-Controlled, Open-Label, Multicenter, Study of Immune Tolerance Induction Performed with rFVIIIFc within a Timeframe of 60 Weeks in Severe Haemophilia A Patients with Inhibitors who have Failed Previous Immune Tolerance Induction Therapies**

**Version: Final 1.0**

**Date: 22/Oct/2020**

## REVISION HISTORY

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| Draft 1.0 | 25/Aug/2017 | [redacted] | New Document |
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# SIGNATURE PAGE – SWEDISH ORPHAN BIOVITRUM

## Declaration

The undersigned has/have reviewed and agree to the statistical analyses and procedures of this clinical study, as presented in this document.

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## SIGNATURE PAGE - PAREXEL

**Declaration**

The undersigned agree to the statistical analyses and procedures of this clinical study.

If this document has been signed electronically, signature(s) and date(s) are present at the end of the document:

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22 OCTOBER 2020

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# ABBREVIATION AND ACRONYM LIST

| | |
|---|---|
| ABR | Annualized Bleeding Rate |
| AC | Annualized Consumption |
| ADM | Annualized Days Missed |
| AE | Adverse event |
| aPCC | Activated Prothrombin Complex Concentrate |
| aPTT | Activated Partial Thromboplastin Time |
| ATC | Anatomical Therapeutic Chemical |
| BLQ | Below the lower limit of quantification |
| BMI | Body Mass Index |
| Bpm | Beats per minute |
| CD4 | Cluster of Differentiation 4 |
| CI | Confidence interval |
| CRF | Case Report Form |
| CS | Clinically Significant |
| CSP | Clinical Study Protocol |
| CSR | Clinical Study Report |
| DBP | Diastolic blood pressure |
| DRM | Data Review Meeting |
| FVIII:C | Factor VIII activity |
| FUFAS | Follow-up Full Analysis Set |
| FVIII | Factor VIII |
| H | High |
| HIV | Human immunodeficiency virus |
| HLA | Human Leukocyte Antigen |
| IR | Incremental Recovery |
| ITI | Immune Tolerance Induction |
| ITIFAS | Immune Tolerance Induction Full Analysis Set |
| L | Low |
| LLOQ | Lower limit of quantification |
| MedDRA | Medical Dictionary for Regulatory Activities |
| NCS | Not Clinically Significant |
| NK | Not known |
| PK | Pharmacokinetics |
| Q1 | First Quartile (25%) |
| Q3 | Third Quartile (75%) |
| rFVIIIFc | Recombinant Coagulation Factor VIII Fc Fusion Protein |
| rVIIa | Recombinant Factor VIIa |

| | |
|---|---|
| SAE | Serious adverse event |
| SAP | Statistical Analysis Plan |
| SBP | Systolic blood pressure |
| SD | Standard Deviation |
| SOC | System Organ Class |
| $t_{½z}$ | Terminal half-life |
| TEAE | Treatment-emergent Adverse Event |
| TFL | Tables, Figures, Listings |
| TPFAS | Tapering Period Full Analysis Set |
| WHO-DD | World Health Organization - Drug Dictionary |

# STATISTICAL ANALYSIS PLAN

The Statistical Analysis Plan (SAP) details the statistical methodology to be used in analysing study data and outlines the statistical programming specifications for the Tables, Figures and Listings (TFLs). It describes the variables and populations, anticipated data transformations and manipulations and other details of the analyses not provided in the Clinical Study Protocol (CSP).

The analyses described are based on the final CSP 3.0, dated, 26/Feb/2018, including Amendment 2 also dated 26/Feb/2018. The analysis of the exploratory laboratory assessments (described in Section 7.5.8 of the CSP) will not be included in the Clinical Study Report (CSR), and will not be described in this SAP.

The SAP will be finalized prior to database lock and describes the statistical analyses as it is foreseen when the study is being planned. If circumstances should arise during the study rendering these analyses inappropriate, or if improved methods of analysis become available, updates to the analyses may be made. Any deviations from the SAP after database lock, the reasons for such deviations and all alternative or additional statistical analyses that may be performed, will be described in a separate SAP Addendum.

## 1. STUDY OBJECTIVES

### 1.1 Primary Objective

- To describe the outcome of immune tolerance induction (ITI) treatment performed with recombinant coagulation factor VIII Fc fusion protein (rFVIIIFc) within a timeframe of 60 weeks in patients who failed previous attempts at tolerization including use of immunosuppressants.

### 1.2 Secondary Objectives

- To describe time to tolerization (i.e ITI success) of ITI performed with rFVIIIFc within a timeframe of 60 weeks in patients who failed previous attempts at tolerization including use of immunosuppressants.
- To describe the relapse rate over a 48-week period following successful ITI performed with rFVIIIFc.
- To describe the intercurrent bleeding during ITI and during the 48-week period after successful ITI performed with rFVIIIFc.
- To describe safety and tolerability of rFVIIIFc when used for ITI.
- To describe the impact of ITI treatment with rFVIIIFc on health economy.
- To describe adherence of rFVIIIFc when used for ITI

### 1.3 Exploratory Objectives

- To explore the mechanism of ITI in patients undergoing ITI performed with rFVIIIFc

## 2. STUDY DESIGN

This is an open-label, single-arm, interventional multi-centre study designed to explore ITI performed with rFVIIIFc within a timeframe of 60 weeks in patients with severe haemophilia A, who have failed previous attempts at tolerization including use of immunosuppressants.

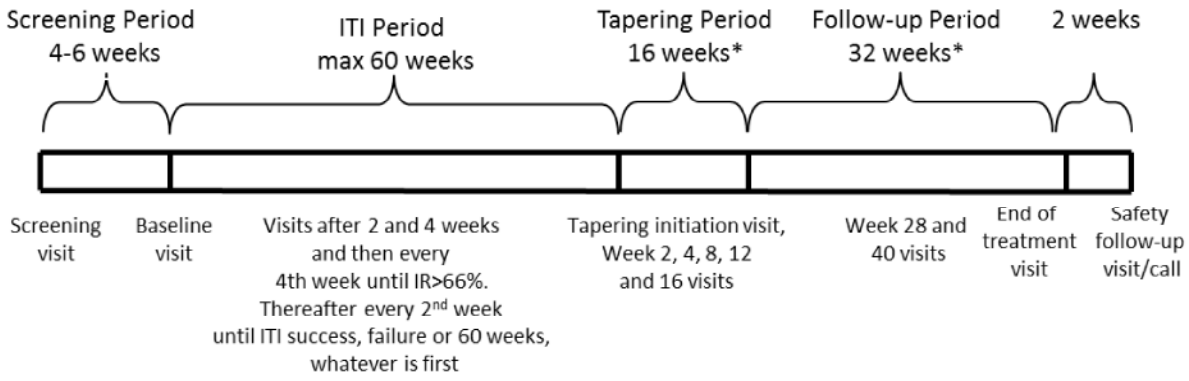
The patient should have undergone at least one failed ITI treatment attempt with the following characteristics:

- A minimum FVIII dose equivalent to the low dose arm of the International ITI study (50 IU/kg, 3 times/week)
- A minimum ITI treatment period of 33 months, or
- Shorter than 33 months if no downward trend of at least 20% in the inhibitor titer in a 6-month period after the initial 3 months of the ITI treatment indicating a stagnation in the tolerization attempt.

The use of immunosuppressant drugs without the combination of the above is not sufficient.

The study will be conducted in 20 patients recruited from countries in Europe and in North America. The study consists of 4 to 6weeks screening period, a maximum 60-week ITI period, a 16-week tapering period and a 32-week follow-up period. Only patients who achieve ITI success will enter the tapering and follow-up periods.

**Figure 1 Study flow chart**




* Only patients who achieve ITI success within 60 weeks

The duration of individual patient study participation will vary based on time to ITI success.

The maximum individual patient study duration is expected to be approximately 116 weeks, i.e., 6 weeks of screening + 60 weeks of treatment +16 weeks of tapering + 32 weeks of follow-up + an additional 2 weeks for safety follow-up.

The minimum individual patient study duration is expected to be approximately 42 weeks, i.e., 4 weeks of screening + 36 weeks of ITI treatment + an additional 2 weeks for safety follow-up.

A detailed Schedule of Events can be found in Appendix 12.1.

# 3. STUDY POPULATION

The study population is planned to consist of 20 male patients of any age, diagnosed with severe haemophilia A, previously treated with any plasma-derived, recombinant conventional or extended half-life FVIII product and with documented failed previous ITI attempt(s). Furthermore, they should have been diagnosed with high titer inhibitor (historical peak ≥ 5BU/mL according to medical records) and have an inhibitor titer ≥0.6 BU/mL at screening.

Detailed lists of inclusion and exclusion criteria are shown in Sections 7.3.1 and 7.3.2 of the CSP.

# 4. STATISTICAL BASIS FOR SAMPLE SIZE

Haemophilia A is a rare disease, hence there is a limited number of patients with severe haemophilia A who have developed inhibitors and have previously failed an ITI treatment attempt. Therefore, no formal sample size calculation was performed. The 20 patients to be included is based on what is estimated to be needed to describe the outcome of ITI within a timeframe of 60 weeks as well as on what is also considered feasible to recruit.

# 5. RANDOMIZATION AND REPLACEMENT

There is only one treatment arm in the study, and no randomization is done. Withdrawn patients will not be replaced, except if they did not receive any dose of IMP.

# 6. STATISTICAL ANALYSIS CONVENTIONS

## 6.1 Analysis Variables

### 6.1.1 Demographic and Other Background Variables

The following demographic and anthropometric information will be recorded at the screening visit:

- Date of informed consent
- Medical history (see Section 6.1.3for details)
- Age at screening
- Gender
- Ethnic origin
- Race
- Height
- Body weight (kg)

Geographic location (Europe/North America) and body mass index (BMI) will be derived.

The weight recording will be repeated at each visit. Height will be measured again at the End of Treatment visit.

### 6.1.2 Exposure and Compliance

#### 6.1.2.1 Treatment Regimen

For each treatment regimen, including the initial regimen and subsequent changes, the following will be recorded in the CRF:

- Start and stop date of regimen
- Status (ongoing or stopped)
- Dose (IU/kg) and dosing frequency
- Reason for regimen change (initiation of ITI, tapering of dose, entering follow-up period, decrease due to high activity levels, dose increase due to low activity levels, other).

#### 6.1.2.2 Exposure to rFVIIIFc

The administration of rFVIIIFc will be recorded in the Case Report Form (CRF) (if at clinic) or in the patient diary (eDiary).

The following information will be captured in the CRF:

- Date and time of injection start
- End time of injection
- If injection was interrupted (recorded at clinic only):
    - Reason why
    - Start time of interruption
    - End time of interruption
- Number of vials injected
- Kit number and nominal IU amount of each vial
- Total nominal IU amount administered
- Reason for injection (baseline injection, incremental recovery (IR) assessment, half-life assessment, training, surgery, treatment of bleed 1$^{st}$ injection, follow-up injection after bleed, other)
- If reason is bleeding, details regarding the bleeding (see Section 6.1.5.5)

The following information will be captured or computed in the eDiary

- Date and time of injection
- Dose injected

- Kit numbers of injected kits and strength of each vial
- Total vials and nominal IU amount administered (calculated by eDiary)
- Reason for injection (e.g. planned injection, 1st injection for treatment of bleed, follow-up injections for treatment of bleed)
- If reason is bleeding, details regarding the bleeding (see Section 6.1.5.5)

The kit numbers, total vials, nominal IU per vial will be recorded, but not mapped to SDTM.

For each dose administration of rFVIIIFc, the variables Days in Study and Days in Period, will be derived as:

Date of Dose Administration – Start Date (of treatment and study period respectively) + 1 day

The number of exposure days will also be derived as number of days since study entry with rFVIIIFc administration up to and including the current administration.

#### 6.1.2.3 Bypassing Agent Prescription

#### 6.1.2.4 Bypassing Agent Administration

All administrations of bypassing agents will be recorded in the same way as recorded for the rFVIIIFc injections (see Section 6.1.2.2), with the addition that the name of the specific bypassing agent product used will be recorded instead of kit numbers. Days in study and days in period will be derived in the same manner as derived for rFVIIIFc.

### 6.1.3 Medical History

Medical, surgical, haemophilia, inhibitor, bleeding and ITI history will be collected and recorded at the Screening Visit.

#### 6.1.3.1 Medical and Surgical History

The medical and surgical history includes any significant medical condition and/or any significant surgical histories, including any other congenital immunodeficiency.

The following information will be recorded for medical and surgical history:

- Body System (as per selection field in eCRF)
- Diagnosis / Condition (verbatim term)
- Start Date and Date of Resolution

- Status (Stopped or Not resolved)

All medical and surgical history will be coded using Version 22.0 of the Medical Dictionary for Regulatory Activities (MedDRA), including System Organ Class and Preferred Term.

#### 6.1.3.2 Haemophilia History

The patient's history of haemophilia will be recorded in the CRF, including the following:

- Date of diagnosis
- Severity of disease (mild, moderate or severe)
- Family history of haemophilia (ideally two generations back), including list of affected relatives (this does not include family members that are only carriers)
- Family history of inhibitors (yes, no or unknown)
- Genotype (information obtained from patient records, if available or tested if given appropriate informed consent), including
    - FVIII mutation (e.g. Intron 22 Inversion, Intron 1 Inversion, etc.)
    - Type of FVIII mutation (if applicable)
    - Mechanism of mutation (if applicable)
    - Human leukocyte antigen (HLA) allotype
- Blood group

Age at diagnosis will be derived. Family history of haemophilia will be classified either as none (no relatives are affected), immediate (siblings, parents or grandparents) or extended (siblings, parents and grandparents do not have the disease, but other relatives do).

#### 6.1.3.3 Prior Haemophilia Treatments

The patient's history of haemophilia treatment at screening will be recorded in the CRF, including the following:

- Number of prior exposure days to FVIII at screening (0-50, 51-100, 101-150, >150 days).
- All treatment regimen of FVIII products and/or bypassing agents in the 12 months prior to the baseline visit, including:
    - Product.
    - Start/End Date.
    - Whether it is ongoing or stopped.

- Total Dose and dose per kg, including level and frequency.
- Type of regimen (on-demand or prophylaxis).

The dose level and frequency for the last treatment will be derived from this recorded data.

#### 6.1.3.4 Inhibitor History

Patient inhibitor history will be recorded, including the following:

- Age at inhibitor development
- Number of exposure days at detection of inhibitor development
- Documented peak inhibitor level
- Date of documented peak level
- Last product used prior to inhibitor development, also including total dose and dose per kg, regimen and schedule (i.e. dose frequency)

#### 6.1.3.5 Bleeding History

The following information will be recorded per patient for any bleeding episode in the last 12 months prior to baseline:

- Date of bleed
- Location of bleed (joint, muscle, internal or skin/mucosa)
- Whether bleed was spontaneous or traumatic
- Treatment details, including:
  - Product used to treat
  - Total Dose (dose and dose unit)

To make comparison easier, if the total dose is given in IU the patient's weight at screening will be used to calculate the total dose in IU/kg and vice versa.

#### 6.1.3.6 ITI History

Previous immune tolerance induction treatments will be recorded, including:

- Start and end date
- Date of inhibitor titer measurement before initiation of ITI treatment
- Titer levels before initiation of ITI treatment
- Date of peak inhibitor level during ITI treatment

- Peak inhibitor level during ITI treatment
- Date of last measured inhibitor level during treatment
- Inhibitor level when stopping the treatment
- Reason for failures
- FVIII Product and dosing details, including:
    - FVIII product used (recombinant, plasma with von Willebrand factor, plasma without von Willebrand factor)
    - Dose and dosing frequency
    - Start and End Date
    - Whether treatment is ongoing
- Duration of any treatment interruption of at least two weeks
- Other immunomodulatory therapies to support ITI, including:
    - Description of therapy
    - Start and End Date
    - Whether therapy is ongoing

#### 6.1.3.7 Allergy History

The history of allergy or anaphylaxis associated with rFVIIIFc, any other FVIII product, recombinant factor VIIa (rFVIIa), activated prothrombin complex concentrate (aPCC) or other plasma products will be specifically recorded, including:

- Product type (e.g. rFVIIa)
- Type of reaction
- Year

#### 6.1.3.8 HIV and Hepatitis Status

Whether the patient is positive for HIV according to the historical medical charts will be entered into the CRF. If the patient is positive, the following will also be recorded:

- Viral load for HIV
- Cluster of differentiation 4 (CD4) cell count
- Platelets
- Whether existing lab results from within last 26 weeks were available for viral load, CD4 cell count and platelets

- If lab results were not available, whether a sample was taken and date of sample
- If sample was not taken even though lab results were not available, reason why

The Hepatitis B and C status (positive/negative) from historical medical charts will be recorded in the CRF.

### 6.1.4 Concomitant Medication and Procedures

Information regarding concomitant medications will be recorded for the patient. Concomitant information for the patient's mother will only be collected if and while she is breastfeeding the patient. Data to be collected includes:

- Name of drug
- Dose and dosing frequency
- Route of administration
- Reason why medication was prescribed (Haemophilia A, medical history, adverse event, vaccination, prophylaxis or other)
- Start and end Date
- Whether medication is still ongoing

All concomitant medication will be coded using the World Health Organization – Drug Dictionary (WHO-DD), version B3 March 2019.

Concomitant procedures will also be recorded, including:

- Name of procedure
- Start and end date
- Reason for the procedure
- If the reason is medical history or adverse event, a reference number will point to the corresponding entry in the CRF

### 6.1.5 Efficacy Variables

#### 6.1.5.1 Inhibitor Titers

Blood sampling for the determination of FVIII inhibitors will be collected at all visits during the study, as described in the Schedule of Events (see Appendix 12.1). The following information will be collected:

- Date and time of sample collection
- Destination of sample (local or central laboratory)
- Result (including unit)
- Whether sample was collected per protocol, and if not, the reason why

#### 6.1.5.2 Assessment of FVIII Activity, Incremental Recovery and Terminal Half-life

The level of FVIII activity (FVIII:C) will be measured according to the Schedule of Assessment in order to evaluate incremental recovery (IR) and terminal half-life ($t_{½z}$). Number and time-point of samples taken depend on whether only IR should be assessed or if both IR and $t_{½z}$ should be determined. The purpose of every sample will be recorded in the eCRF.

A single monitoring sample of FVIII:C will be taken at each visit where IR or $t_{½z}$ are not assessed, starting from Week 2. Once negative titer has been confirmed, at the following visits IR will be assessed after rFVIIIFc injection with the same dose as currently prescribed (single dose not total dose per day), and two FVIII:C samples (within 30 minutes prior and 30 (±5) minutes post dose respectively) will be taken.

After IR > 66% of the expected IR has been confirmed the assessment of terminal half-life ($t_{½z}$) will be done at each consecutive visit (until terminal half-life $t_{½z} \geq 7$ hours). The FVIII:C samples will be drawn within 30 minutes prior and 30 (±5) minutes, 24 hours, 30 hours and 48 hours (±60 minutes) after a rFVIIIFc injection with the same dose as currently prescribed. In all cases, FVIII:C will be converted to IU/dL A percentage of 100% corresponds to a dose of 100 IU/dL.

##### 6.1.5.2.1 Assessment of FVIII:C

A blood sample will be collected. The following information will be recorded:

- Date/Time of sample collection
- Destination of sample (central or local laboratory)
- If a sample was not taken, reason why
- Method used [one-stage activated partial thromboplastin time (aPTT) or chromogenic substrate assay, only for local lab]
- Result

In addition, time since last dose will be derived for FVIII:C assessments, as date/time of sample collection less date/time of last dose in hours and minutes (hh:mm).

#### 6.1.5.2.2 Assessment of Incremental Recovery (IR)

The information described in Section 6.1.5.2.1 will also be recorded for both the pre-injection and the post-injection sample. In addition, the following will also be recorded:

- IR (IU/dL per IU/kg), as calculated by the investigator or designee
- Expected IR(IU/dL per IU/kg) (per investigator judgement)
- Whether calculated IR > 66% of the expected IR, as per judgement of investigator

As the investigator will calculate incremental recovery based on the local laboratory results, a second incremental recovery will be derived on the basis of the central laboratory results, in the same manner as described in the CSP:

$$IR = (C_{30min} - C_{predose}) / Dose\ [IU/kg]$$

Concentrations below the lower limit of quantification will be replaced by zero for this calculation. The expected IR as entered by the investigator will be used to derive the ratio of observed to expected IR.

#### 6.1.5.2.3 Determination of Terminal half-life ($t_{½z}$)

For the assessment of the terminal half-life ($t_{½z}$), the information described in Section 6.1.5.2.1 will also be recorded for all samples. In addition, incremental recovery will be assessed as described in Section 6.1.5.2.2 and the following information will also be recorded:

Terminal half-life ($t_{½z}$) will be calculated for both the local laboratory results (main endpoint) and the central laboratory results.

The elimination half-life will be calculated from the corrected estimated terminal slope ($\lambda_z$) of the log – linear *FVIII:C* versus time curve, i.e. $t_{1/2z} = 0.693 / \lambda_z$. Estimation of the terminal slope will be based on at least three observational data points.

The calculations of elimination half-life will be performed as follows:

(i) Estimate the uncorrected terminal slope ($\lambda$) from the observed FVIII:C *vs* time data

(ii) Calculate the residual activity from the previous dose still present at each of the last 3 sampling time points, i.e. at 24, 30 and 48 hours post-dose;
Residual activity at time t = FVIII:$C_{pre\ dose} \cdot e^{-\lambda \cdot t}$

(iii) Subtract the residual activity from the observed FVIII:C at each time point

(iv) Estimate the elimination half-life from the ”corrected” FVIII:C *vs* time data

All individual FVIII:C versus time data sets will be analysed by non-compartmental analysis (NCA) using Phoenix WinNonlin v. 6.3.

#### 6.1.5.3 ITI Outcome

Patients may achieve 1 of 4 ITI outcomes:

1. ITI success
2. Partial success
3. Treatment failure
4. Not determinable due to withdrawal during the ITI period.

The ITI outcome will be derived for every patient.

**ITI Success**

The following criteria (1, 2 and 3) have to be fulfilled at the same time within 60 weeks for a patient to be considered having achieved ITI success:

1. Negative inhibitor titer (< 0.6 BU/mL) at two consecutive visits
2. Calculated IR > 66% of the expected IR at two consecutive visits
3. Terminal Half-life ($t_{½z}$) ≥ 7 hours

Whether ITI success has been achieved and the date on which each of the three criterions has been met will be recorded.

**Partial Success**

Partial success is defined as fulfilling the first criteria and either the second or the third. The criteria do not need to be fulfilled at the same time. Patients who fulfil all three success criteria but not at the same time, are also counted for partial success. Partial success will only be determined for patients who have

completed the maximum period of 60 weeks of ITI but do not fulfil the criteria for ITI success or treatment failure.

**Treatment Failure**

Treatment failure is defined as fulfilling one of the following three criteria:

1. No downward trend of at least 20% in the inhibitor titers in the six (6) months after the initial three (3) months of ITI treatment
2. Presence of a sustained positive inhibitor (≥ 0.6 BU/mL) after 60 weeks of ITI
3. Negative inhibitor titer without either achieving IR > 66% of expected IR or Terminal half-life $t_{½z} \geq 7$ hours after 60 weeks of ITI

For each patient who fulfils at least one of the three criteria, the one with the lowest criterion number will be considered to be the primary reason for failure.

**Not determinable due to withdrawal during the ITI period**

A patient, who is withdrawn from the study treatment and discontinues the study before completion of the ITI period for any one of the reasons described in Section 7.3.3 of CSP, will have the ITI Outcome "Not determinable due to withdrawal during the ITI period".

#### 6.1.5.4 Relapse

Relapse in the tapering or follow-up period is defined as the occurrence of any of the following (with or without clinical symptoms) after complete ITI success:

1. Positive inhibitor (≥0.6 BU/mL), on two consecutive assessments performed within 2-4 weeks

   AND

2. An IR ≤ 66% of the expected IR, on two consecutive assessments performed within 2-4 weeks

For relapse the date at which relapse criteria was met will be recorded.

The time in days between relapse and ITI success will be derived, as the difference between the two dates.

#### 6.1.5.5 Bleeding

All bleeding episodes will be recorded in the patient diary or in the CRF, including the following:

- Date/time of bleed
- Type of bleeding (spontaneous or traumatic)
- Whether bleeding was related to sports/physical activity
- Location of bleeding

### 6.1.6 Safety Variables

#### 6.1.6.1 Adverse Events

In a clinical investigation, an adverse event (AE) is defined as any untoward medical occurrence in a patient administered a pharmaceutical product which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. Any progression/worsening of the underlying disease is also considered to be an AE. An AE is considered serious if it meets one or more of the following criteria:

- Results in death
- Is life-threatening (i.e., at immediate risk of death)
- Requires in-patient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect (i.e., in an offspring to the study patient)
- Any other event that the investigator or company judges to be serious

Specifically, for this study, the following medically important events are also considered to be serious:

- Development of a confirmed positive inhibitor (>0.6 BU) during the tapering or follow-up periods
- A patient develops a Grade 2 or greater allergic reaction in association with administration of rFVIIIFc defined as follows using the Recommendations for Grading of Acute and Subacute Toxic Effects on the WHO scale
  - Grade 2: bronchospasm; no parenteral therapy needed
  - Grade 3: bronchospasm; parenteral therapy required
  - Grade 4: anaphylaxis

- A patient develops a vascular thrombotic event, with the exception of IV injection site thrombophlebitis

In this patient population, bleeding episodes are not considered AEs, but if they meet a serious criterion they should be reported as a serious adverse event (SAE). Bleeding episodes that occur outside the clinic will be captured in the patient diary. Any relapse after successful ITI will also be captured as an SAE.

All AEs will be coded using MedDRA Version 22.0, including System Organ Class (SOC) and Preferred Term (PT).

A treatment-emergent adverse event (TEAE) is defined as an AE that begins or that worsens in severity after at least one dose of the study drug has been administered.

Any AEs with incomplete start and end dates/times will be treated as follows:

- Adverse events with unknown start and/or end times (but where the date is known) will be imputed with a time of 00:00 h for the tabulations but will be shown as NK:NK in the listings (where NK = Not Known).
- Adverse events with completely unknown start dates will be considered as treatment-emergent for the tabulations and will be shown as NK in the listings.

The following information will be recorded for AEs:

- Start and End Date
- Description of event (verbatim term)
- Status (stopped or not resolved)
- Severity (mild, moderate or severe)
- Relationship to study drug (related or not related according to investigator's judgement)
- What treatment was required (none, concomitant medication or other therapy)
- Whether it resulted in patient being terminated from the study
- Whether the AE was serious, and applicable seriousness criteria
- In case of death, whether autopsy was performed

The reporting period for AEs is described in Section 7.5.6.1.2 of the CSP. All SAEs experienced between informed consent and safety follow-up will be recorded, as well as any non-serious AEs between first dose of IMP and the safety follow-up visit.

#### 6.1.6.2 Clinical Laboratory Tests

Blood samples will be collected according to the Schedule of Events (see Appendix 12.1) at screening, baseline visit and then every 12$^{th}$ week from start of the ITI treatment period until the end of tapering period. Blood and urine samples will also be collected at the end of treatment visit. The date of collection will be recorded in the CRF.

Hematology includes white blood cell count and differential, red blood cell, hemoglobin, hematocrit, and platelet count.

Blood chemistry includes sodium, potassium, chloride, total protein, total bilirubin, gamma glutamyl transferase, aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, blood urea nitrogen, serum creatinine, and glucose.

Urinalyses includes dipstick for blood, protein, and glucose. If the protein reading is positive (≥1+), a full laboratory urinalysis, i.e. microscopic sediment evaluation will be required. Further investigation based on the dipstick and microscopic sediment results should be according to the investigator's discretion.

Samples will be analysed at a local laboratory.

Any clinically significant abnormal laboratory values will also be reported as AEs, and for those the following will be recorded in the CRF:

- Date of blood/urine collection
- Result of laboratory variable assessed
- Normal ranges at the local laboratory
- Adverse Event reference number

Laboratory values that are not both abnormal and clinically significant will not be recorded in the CRF.

#### 6.1.6.3 Vital Signs

The following vital signs measurements will be obtained at each visit according to the Schedule of Events (see Appendix 12.1).

- Systolic blood pressure (SBP) [mmHg]
- Diastolic blood pressure (DBP) [mmHg]
- Respiratory rate [breaths/minute]
- Pulse rate [beats per minute (bpm)]
- Body temperature (tympanic) [°C]
- Weight [kg]

Date and time of assessment will also be recorded. Clinical significant abnormal vital signs will be recorded as AEs.

#### 6.1.6.4 Physical Examination

A general physical examination will be assessed and recorded according to the Schedule of Events (see Appendix 12.1). The body systems skin, lymph system, neck, chest/lungs, heart, vascular system, abdomen, musculoskeletal and neurological will be assessed as normal or abnormal. Abnormalities will be described. Any abnormalities reported at baseline will be recorded as medical history. New abnormalities or worsening of baseline abnormalities after the baseline visit will be recorded as adverse events.

### 6.1.7 Pharmacokinetic Variables

Unless otherwise stated, derivation of pharmacokinetic (PK) parameters will be the responsibility of Quantitative Clinical Development (QCD), PAREXEL International. Only PK parameters necessary for the evaluation of treatment success will be considered. The following PK parameters will be determined:

**Table 1 Pharmacokinetic Parameters after Repeated Dose Administration**

| Parameter | Definition |
|---|---|
| $t_{½z}$ | Terminal Half-life (hours) |
| IR*# | Incremental recovery (IU/dL per IU/kg) |

*

* Will be directly calculated and entered into the CRF by the investigator.

\# Will be calculated and reported using data from both local and central laboratory

#### 6.1.7.1 *Pharmacokinetic Parameter Calculation Methods*

PK parameters will be calculated by non-compartmental analysis methods from the activity-time data using WinNonlin (WNL) Professional (Version **6.3 or higher**) following these guidelines:

- Actual sampling times relative to dosing rather than nominal times will be used in the calculation of all derived PK parameters.
- There will be no imputation of missing data.
- All below the limit of quantification (BLQ) values pre-dose will be substituted by zeros. Terminal BLQ values will be disregarded.

The calculation of the PK parameters is described in Section 6.1.5.2.

### 6.1.8 Pharmacoeconomic Assessments

Consumption will be assessed based on amount of administered drug as recorded in the CRF and in the diary.

Days missed from school or work will be recorded in the diary. The last day for consecutive span of missed days will be derived using start date and number of consecutive days after the first.

Hospitalizations will be recorded including start and end dates and will also be captured as SAEs. The number of days per hospitalization will be calculated as ‘end date’ – ‘start date’ + 1 (days).

## 6.2 Analysis Populations

The final assignment of the patients to the different analysis populations will be made during the Data Review Meeting (DRM) before database lock and statistical analysis, based upon the criteria described in this section. In general, it is not planned to exclude any patient from any analysis set, as long as they reach each period respectively.

### 6.2.1 ITI Full Analysis Set

The ITI full analysis set (ITIFAS) will include all patients receiving at least one dose of rFVIIIFc and will be used for describing efficacy and safety during ITI treatment.

### 6.2.2 Tapering Period Full Analysis Set

The tapering period full analysis set (TPFAS) will include all patients who achieve ITI Success and enter the tapering period of the study. All analyses describing efficacy and safety during this period will be based on this analysis set. In addition, some of the analyses (e.g. bleeding and hospitalization) combine the tapering period and the follow-up period (described in Section 6.2) into a longer, 48-week follow-up period. The TPFAS will be used for these analyses as well.

The tapering period is defined to start at the visit after confirmed ITI success.

### 6.2.3 Follow-up Full Analysis Set

The follow-up full analysis set (FUFAS) will include all patients will include all patients who achieve ITI Success and enter the follow-up period in the study. Note that most analyses describing efficacy and safety during this period will be based on combined 48-week follow-up period mentioned in Section 6.2.2 instead. The FUFAS will be used for the generation of tables summarizing consumption.

The start of the follow-up period is defined as the day after the date of the last recorded visit in the tapering period.

## 6.3 Statistical Analysis Methods

### 6.3.1 Listings and Descriptive Statistics

All original and derived parameters as well as population characteristics will be listed. Relevant parameters will further be described using summary statistics.

Frequency counts (number of patients [n] and percentages) will be made for each qualitative variable. Missing values will be treated as a separate category.

Descriptive statistics (n, mean, standard deviation [SD], median, first and third quartile [Q1 and Q3], minimum and maximum) will be calculated for each quantitative variable (unless otherwise stated). The number of missing values will also be displayed.

All data that can be recorded in either the CRF or the patient diary (e.g. bleeding episodes) will be combined without regard to source in summary tables. In listings it will be indicated whether the entry is from the CRF or whether it is from the patient diary.

All listings will include repeated and unscheduled measurements.

The following rules will apply to any repeated measurements:

- If the repeated measurement occurs prior to the first dose of study drug, then the last obtained value of any repeated measurement before first dose will be used in the descriptive statistics.
- If the repeated measurement occurs after the first dose of study drug, then the original value of any repeated measurements will be used in the descriptive statistics.

#### 6.3.1.1 *Definition of Visit for Summary Tables*

Two different definitions of visit will be used in the following sections.

- Nominal visit as recorded in the CRF:
    - Screening
    - Baseline
    - ITI Period, Week 2
    - Interim ITI Visit, Week 4 up to Week 60
    - ITI Assessment Visit 1 to 30
    - Tapering Period Visit Week 2 up to Week 16
    - Follow-up Visits Week 28 and Week 40
    - End of Treatment Visit
    - Final Safety Follow-up
- Time-based visit:
    - Visits for Screening and Baseline, visits in the tapering or follow-up period, the End of Treatment visit and the Final Safety Follow-up visit will be the same as for nominal visits
    - Visits in the ITI period, prior and including the visit where the first negative titer was measured will be mapped based on the nominal week number, for example ”ITI Visit – Week 4” will be mapped to “ITI Period – Week 4”
    - Visits in the ITI Period will be mapped as follows:

- The Baseline and the Week 2 Visit will be retained as is
- All other scheduled visits will be mapped to the closest even number of weeks, i.e. if a Visit takes place on Day 79 (with Day 1 being the day of treatment start), then it will be mapped to "ITI Period – Week 12". In general, the week will be determined by calculating 2 times the rounded integer result of (Visit Date – Treatment Start)/14. If two visits will be mapped to the same even number of weeks, only the first one will be used in summary statistics.

- No summary statistics will be shown for unscheduled and optional visits (i.e. visit in Week 20 of tapering period if period is prolonged). In listings unscheduled visits will be shown with period, study day and study week (defined as study day/7 rounded up).

If not explicitly stated otherwise, the term "visit" will refer to nominal visit. The mapping of visits that took place outside of the allowed window visit, defined in the CSP, will be discussed in the DRM.

### 6.3.2 Rounding and Decimal Places

The following rules will be followed with regard to the number of decimal places and presentation of data in the tables and listings of all data:

1. All data will be listed according to the number of decimal places presented in the source data.
2. Mean, median, Q1, Q3 and standard deviation will be tabulated to one more decimal place than the source data.
3. Minimum and maximum values will be tabulated to the same number of decimal places as the source data.
4. A maximum of three decimal places will apply to all summary statistics.
5. Percentages for frequencies will be displayed with 1 decimal place.
6. Percentage change of baseline will be displayed with 0 decimal places; for statistics of percentage change of baseline (e.g. mean and SD) the rules above apply.
7. Annualized event rates will be displayed with 1 decimal place; for statistics of annualized event rates the rules above apply.

### 6.3.3 Statistical Significance Level

No formal statistical tests will be performed, and no confidence intervals will be presented. Therefore, it is not necessary to specify a significance level.

### 6.3.4 Software

All statistical analyses will be performed using Statistical Analysis Software (SAS®) Version 9.3 or higher.

The PK analysis will be performed using WinNonlin Professional Software Version 6.3 or higher.

### 6.3.5 Missing Data

There will be no imputation of missing data.

### 6.3.6 Interim Analysis

No formal interim analysis is planned. Baseline data may be reported when available.

### 6.3.7 Protocol Deviations

PAREXEL Biostatistics and Sponsor will determine the deviations to be included in the CSR and the impact classes of deviations will have on the final datasets. Both PAREXEL Biostatistics and Sponsor have input into, and review, the Protocol Deviation Specifications and Protocol Deviation Report throughout study life cycle and review/reconciliation of deviations.

All protocol deviations will be recorded by the Investigator.

A first determination of whether protocol deviations should be considered major or minor will be performed internally at PAREXEL (e.g. physician, Data Manager, Biostatistician, Pharmacokinetic (PK) Scientist/Analyst and Medical Writer), based upon the Protocol Deviation Specifications, Version 2.0, dated 22-Jan-2019 or later if an update is made between DRM and finalization of this SAP. During the data review meeting (DRM) and before database lock, protocol deviations and their classification as major or minor will be discussed with the responsible study team at the Sponsor

Time window deviations will be listed, including procedure, actual time, scheduled time and deviation (if feasible to calculate). An additional listing will show all other protocol deviations, including description, date, category, classification (major/minor) and consequent exclusions from specific analyses (if any).

### 6.3.8 Disposition

Disposition data will be displayed using the ITIFAS.

The patient disposition will be summarized as follows:

- Number of patients dosed.
- Number of patients who completed each period.
- Number of patients who withdrew within each period, including reason of withdrawal.
- Number of patients who were discontinued due to not achieving ITI success in the ITI period by unfulfilled success criteria (see Section 6.1.5.3).
- Number of patients who completed the end of treatment visit.
- Number of patients who were discontinued due to relapse in the tapering period.
- Number of patients assigned to each analysis population.

Date of informed consent, withdrawals and the assignment of patients to the different analysis populations will also all be listed.

### 6.3.9 Demographic Data

The following demographic data will be listed and summarized using the ITIFAS: age, geographic location, weight, BMI and height at screening, gender, race and ethnic origin. In addition, height at the End of Treatment visit will be included in the listing.

### 6.3.10 Medical History

The ITIFAS will be used for all listings and summary tables which are related to medical history. For each of the following subsections, the data will be listed, including the variables described in Section 6.1.3.

#### 6.3.10.1 Haemophilia History Including Treatments

The following summaries will be presented for the history of haemophilia:

- Summary table, including counts and frequencies for severity of haemophilia, as well as family history and descriptive statistics for age at diagnosis

- Summary table, including:
    - Descriptive statistics for total consumption (IU and IU/kg) of FVIII in the last 12 months – overall and stratified by whether taken concomitantly with bypassing agents
    - Absolute and relative frequencies for different FVIII products
    - Absolute and relative frequencies for the use of by-passing agents in the last 12 months
    - Descriptive statistics for the total consumption of bypassing agents – overall and stratified by whether taken concomitantly with FVIII products
- Blood groups and genotyping, including counts and frequencies of different FVIII mutation types, mechanism and HLA allotypes. The FVIII mutation and HLA allotyping summary will not consider whether the data is collected from existing medical records or from samples analysed at central laboratory.

For summaries of consumption, a subject who did not take that specific product will be counted as having a consumption of zero.

#### 6.3.10.2 Inhibitor History

The following summary will be presented for the history of inhibitor development:

- Absolute and relative frequencies for:
    - Last product used prior to inhibitor development
    - Last dosing frequency prior to inhibitor development
- Descriptive statistics for:
    - Exposure days at first inhibitor development
    - Last weekly dose prior to inhibitor development
    - Historical peak titer levels
    - Age at inhibitor development

- Time between first inhibitor development and start of rFVIIIFc treatment in this study, estimated as the difference between age at start of treatment and age at first inhibitor development

#### 6.3.10.3 ITI History

The following ITI history summary will be presented for all previous ITI attempts:

- Absolute and relative frequencies for:
  - Number of ITI attempts
  - ITI treatments products (FVIII and Other) used in at least one ITI attempt for the patient. In addition, the absolute frequency per product counted by ITI attempt instead of per subject will be given
  - Reason for ITI treatment failures (per subject and for absolute frequencies also per attempt)
- Descriptive statistics for:
  - Number of ITI attempts, duration, dosing/factor consumption, outcomes (bleeds), inhibitor titer before start of ITI, duration of ITI attempts, attempts with and without concomitant use of bypassing agents, peak inhibitor during treatment and inhibitor at end of treatment (only the last treatment per patient will be considered)

All treatment attempts will be listed. This listing will also display the number of recorded historical bleeds that started during the treatment attempt and whether bypassing agents use was also recorded for the time span of the attempt (any overlap counts).

#### 6.3.10.4 Bleeding History

The following summary will be presented for history of bleeding using the ITIFAS:

- Descriptive statistics calculated for the total number of bleeding episodes per patient and counts and frequencies of bleeding during the last 12 months per location, cause and treatment

#### 6.3.10.5 HIV and Hepatitis Status

The patient HIV and Hepatitis status will be listed using the ITIFAS, including the variables listed in Section 6.1.3.8.

#### 6.3.10.6 Allergy History

The history of allergy to FVIII products and other products like bypassing agents will be summarized, showing:

- Counts and frequencies per product type and type of reaction

Other allergies will be included as general medical history.

#### 6.3.10.7 Other Medical History

Medical and surgical history will only be listed, including allergies not covered by Section 6.3.10.6.

### 6.3.11 Concomitant Medication

All concomitant medication will be listed including medical coding and summarized using Anatomical Therapeutic Chemical (ATC) categories, levels 2 and 4. For the purpose of both listing and summary the medication given to the breastfeeding mother will be considered concomitant medication. Whether the medication was given to the patient or the breastfeeding mother will be displayed in the listing.

The ITIFAS will be used for these outputs.

### 6.3.12 Analysis Related to the Primary Objective

#### 6.3.12.1 ITI Treatment Outcome

The number and proportion of patients achieving each of the ITI success criteria, overall ITI success, partial success and treatment failure will be calculated and displayed in a summary table.

Partial success will also be further subdivided, depending on whether the second or the third criterion for success was achieved.

Treatment Failure will also be further subdivided by primary reason of failure, using the treatment failure criteria defined in Section 6.1.5.3.

Prognostic factors for ITI success will be summarized stratified by ITI outcome. Prognostic factors to consider include; historical peak inhibitor titer, pre-ITI inhibitor titer, factor VIII genotype, peak inhibitor titer on ITI, number of previous ITI attempts, time between inhibitor development and start of ITI. In this summary, patients will be included according the best ITI outcome they achieve (partial success is not also counted as failure and complete success is not also counted as partial success). The following categorical variables will be derived for this summary:

- Historical Peak Inhibitor Titer <200 BU (yes/no)
- Pre-ITI Inhibitor Titer <10 BU (yes/no)
- >5 Years between Diagnosis of Inhibitor and Start of ITI (yes/no)

The ITIFAS analysis set will be used for this analysis.

A figure will be presented showing the number and percentages of patients by ITI outcome versus time (up to Week 60, patients will be counted for each time point after their ITI outcome has been determined, regardless of discontinuation or relapse).

In addition, a treatment outcome listing will be produced, displaying for each patient:

- Outcome (ITI success, partial success, failure or not determinable [if withdrawal due to other reasons prior to 60 weeks])
- Study day each of the success criteria was met (blank if not met)
- Relapse (no or relapse criteria met)
- Days after ITI success to relapse

#### 6.3.12.2 FVIII:C Levels

For the FVIII:C the following listings will be produced:

- All local laboratory FVIII:C measurements, including period, visit, assay used, date, nominal and actual time, purpose of sample and result (absolute value for all samples).

- All determinations of incremental recoveries, based on results from local laboratory including period, visit, date, observed and expected IR (incl. units), and ratio of observed to expected IR (as percentage) (see Section 6.1.5.2.2 for derivation). Determinations that indicate either confirmed IR ≥ 66% of the expected IR, ITI success (complete or partial) or relapse will be flagged for the recorded observed/expected percentage. The listing will also contain whether the investigator considered the IR to be ≥ 66% and flags where this contradicts the derived ratio.

- All determinations of terminal half-life, based on results from local laboratory, including period, visit, date and the calculated terminal half-life. Determinations that indicate either confirmed half-life ≥ 7 hours, ITI success (complete or partial) or relapse will be flagged.
- If the measured FVIII:C is below the LLOQ, it will be indicated as BLQ in any listing.

The ITIFAS analysis set will be used for the listings. A figure will show the FVIII:C versus Study Day, with different symbols to indicate assay type and different colours to indicate time point relative to dose.

#### 6.3.12.3 Central and Local Laboratory Comparison

As an exploratory analysis, the following summary tables will be presented using the ITIFAS:

- 2x2 table of local vs central laboratory on observed IR > 66% of the expected IR
- 2x2 table of local vs central laboratory on terminal half-life ($t_{½z}$) ≥ 7h
- 2x2 table of local vs central laboratory on inhibitor titer < 0.6 BU/mL

Both the local and central laboratory results will also be listed; IR and ($t_{½z}$) will be listed together. A separate listing will be shown for the inhibitor titer comparison.

For both FVIII:C and titer levels scatter plots will be presented by period and visit, showing the local laboratory results on the x-axis and the central laboratory results on the y-axis. A line with intercept zero and slope one will be added to indicate a perfect fit. Any BLQ values will be shown at zero.

#### 6.3.12.4 Titer Levels

Absolute values, change from baseline and percent change of baseline of the inhibitor titers will be listed, including all the variables in the CRF (see Section 6.1.5.1). In addition, period and visit will be included and used for chronologically sorting of the listing. The measurements will be flagged, if they indicate one of the following:

- Confirmed negative titer
- Relapse (criteria 1 in Section 6.1.5.4)

The titers (absolute values, change from baseline and percent change from baseline) will also be summarized descriptively by time-based visit for the ITI period. Values below the lower limit of the quantification (LLOQ) will be displayed as BLQ (below the lower limit of quantification) in listings and

treated as zero for the calculation of change from baseline, percent change from baseline and any descriptive statistics.

In addition, the following figures will be produced for the ITI period only:

- Titers versus actual study week by patient in linear scale and semi-logarithmic scale
- Mean titers (± standard deviation) versus nominal time in linear scale and semi-logarithmic scale

The standard deviation will be shown in linear scale only.

As patients leave the ITI period after a different amount of time, the mean figures will be produced for a full 60 weeks after study start, and values for patients that are no longer in the ITI-period due to ITI success will be replaced with zero, including those cases where the subjects relapse within the tapering/follow-up period. The same will be done for any values that are below the LLOQ.

Since the frequency of visits depend on the titer levels, time-based visit (see Section 6.3.1.1) will be used for the mean plot.

The baseline visit measurement will be used to calculate changes from baseline.

The ITIFAS analysis set will be used for the listings, the summary tables will be produced using the analysis set that corresponds the period being displayed.

### 6.3.13 Analysis Related to the Secondary Objectives

#### 6.3.13.1 Time to ITI Success

Time to ITI success in weeks will be analysed with descriptive summary statistics. The same will be done for patients achieving confirmed negative titer, confirmed incremental recovery > 66% of the expected IR and the time until terminal half-life criteria is met respectively. For the descriptive analysis, the time for a patient who either never reaches the criteria or for whom the criteria are never assessed due to not fulfilling the required condition will be considered to be missing.

Time [week] to ITI success will also be analysed descriptively using Kaplan-Meier estimates including median, 25$^{th}$ and 75$^{th}$ quantile. It is considered likely that it will not be possible to provide estimates for the median and the quantiles, due to the success rate not being high enough and the proportion of censored data being too high. Each subsequent week then starts on the seventh day after the first day of the previous week.

Patients who do not achieve ITI success will be treated as follows:

- Patients who discontinued because there was no downward trend of 20% in titers will be considered censored at the time of treatment failure.
- Other patients are considered to be censored at the last observed time. This includes patients who withdrew due to safety concerns or who did not achieve the criteria for ITI success within 60 weeks of starting ITI with rFVIIIFc.

A Kaplan-Meier plot of the cumulative probability of success function will be generated by using the PROC LIFETEST in SAS software.

The following code (or similar code) will be used:

```
PROC LIFETEST DATA = iti_success PLOTS = SURVIVAL;
  TIME success_time * censored (1);
RUN;
```

The same analysis will also be done for the following:

- Time to confirmed negative titer
- Time to confirmed incremental recovery >66% of the expected IR

The ITIFAS analysis set will be used for this analysis. Week for the purpose of this analysis will be defined as follows: the study day/7, rounded up.

#### 6.3.13.2 Occurrence of Relapse

The occurrence of Relapse, as defined in Section 6.1.5.4, during the tapering or follow-up period will be summarized descriptively by calculating the proportion of patients with ITI success who reaches the criteria for relapse. The TPFAS analysis set will be used.

In patients who are relapsing, the time between ITI success and the relapse will also be summarized descriptively.

#### 6.3.13.3 Number of Bleedings during ITI treatment

Bleeding episodes during ITI treatment will be summarized per month as follows:

- Number of bleeding episodes (also shown for the entire treatment period)

- Number and percentage of patients experiencing at least one bleeding episode (also shown for the entire treatment period)
- Number and percentage of patients and total number of bleeding episodes for spontaneous and traumatic bleedings (also shown for the entire treatment period)
- Number and percentage of patients and total number of bleeding episodes by anatomical location (also shown for the entire treatment period)
- Patient bleeding event rate: total bleeds per month (minimum, maximum, median, mean, Q1, Q3 standard deviation). Patients without bleeding are included as a zero count

For the purpose of this analysis, each month is defined as Number of Days/30. Bleeding episodes are counted in the month based on start date. Study Day 1 is the first day of the first month.

In addition, annualized bleeding event rates (ABR) will be displayed, defined for each patient as follows:

$$\text{ABR} = \text{ev}\frac{365.25}{\text{length of ITI period in days}}$$

Here, ev is number of events for the specific patient.

The ITIFAS analysis set will be used for this analysis.

All bleeding episodes during the study (regardless of period) will be listed individually. The period in which the bleeding event occurred (based on start date) will be indicated in this listing.

An additional listing will show the total number of bleeding episodes per month and location and total for each patient in the ITI Period.

#### 6.3.13.4 Bleeding Rate During 48-week Follow-up Period

Descriptive statistics for the bleeding episodes during the 48-week follow-up period (including tapering period) will be displayed using the TPFAS analysis set.

In addition, annualized bleeding event rates (ABR) will be displayed, defined for each patient as follows:

$$\text{ABR} = \text{ev}\frac{365.25}{\text{length of follow-up period in days}}$$

Here, ev is number of events for the specific patient.

#### 6.3.13.5 Consumption

The total study drug consumption as well as the total consumption of bypassing agents will be calculated for each patient by period and listed using the respective period analysis sets. Consumption will also be summarized by period (in the standard absolute dose and dose/kg for the respective product) using the ITIFAS. The consumption for 'other' (per eCRF) bypassing agents will only be summarized, if at least 3 subjects took the specific product.

An additional listing will show the consumption of rFVIIIFc, Novoseven® and FEIBA® in the ITI period.

For the ITI Period, the Tapering Period and the Follow-up Period annualized consumption (AC) will also be calculated and summarized:

$$\mathrm{AC} = \mathrm{CP}\frac{365.25}{\text{length of period in days}}$$

Here, CP is the total consumption of the period in that study.

#### 6.3.13.6 Number of Days Missed School or Work During ITI Treatment

The number of days missed during ITI treatment will be listed and summarized descriptively using the ITIFAS set. The listing will also include later periods. The total number of missed days in the ITI Period will be annualized as described in Section 6.3.13.5.

#### 6.3.13.7 Number of Days Missed School or Work During a 48-week Period Following Successful ITI Treatment

The number of days missed during the 48-week follow-up period (including tapering period) will be summarized descriptively using the TPFAS set. An annualized number of days (ADM) missed will also be displayed, calculated as described in Section 6.3.13.5.

#### 6.3.13.8 Number of Hospitalizations During ITI Treatment

The ITIFAS set will be used to list and summarize the number and total length of hospitalizations during the ITI treatment. This summary will be presented together with that of number of days missed described above. Descriptive statistics for the number of days hospitalized will be calculated and summarized in two different ways:

1. Patients who were not hospitalized are counted as having been hospitalized for zero days

2. Patients who were not hospitalized are considered missing for the calculation of days hospitalized

The listing will also include later periods. The total number of hospitalizations in the ITI Period will be annualized as described in Section 6.3.13.5.

#### 6.3.13.9 Number of Hospitalizations During a 48-week Period Following Successful ITI Treatment

The TPFAS set will be used to summarize the number and total length of hospitalizations during the ITI treatment. Both number and total length will also be annualized in the same manner as described in Section 6.3.13.4. This summary will be presented together with that of number of days missed school or work as described above.

#### 6.3.13.10 Adherence

Adherence will be calculated in two ways as follows:

- Dose adherence: dose administered as registered in diary / doses prescribed
- Frequency adherence: number of days with infusions as registered in the diary / number of days on which infusion was prescribed

Dose prescribed will be taken from the CRF. The frequency as entered in the CRF will also be used for the calculation of number of days on which dose was prescribed.

The number of doses administered will be calculated from the data entered into the eDiary and the eCRF.

This calculation will be done for each period, and the results will be listed and summarized descriptively using the respective period specific analysis set. For the calculation of dose adherence also see also Section 6.3.14 on the handling of doses recorded in duplicate (entered in both subject diary and CRF).

### 6.3.14 Exposure

All doses of rFVIIIFc will be listed using the ITIFAS, including date, time, purpose of dose, total dose, number of vials and kit numbers. A similar listing will be produced for bypass agents, including date, time, product, purpose of dose and amount of dose. Both doses given on-site and recorded in the patient diary will be included.

A summary table will be presented, showing descriptive statistics for the duration of exposure (date of last treatment – date of first treatment) and the total number of exposure days (sum of days with exposure).

In addition, all treatment regimens (including the derived first) will be listed for each patient including start date, stop date, dose (IU/kg), dosing interval and reason for regimen change. There will be an additional listing, including only treatments regimens during the follow-up period, using the FUFAS.

A figure will present weekly dose amount (IU/kg) versus time by patient (spaghetti plot) for the tapering period using the TPFAS analysis set.

Each dose should be entered only in the eCRF OR in the patient diary, but it is possible that it is entered in both by mistake. In this case, an attempt will be made to identify and flag duplicated dosing entries, as follows: two doses are considered duplicates, when:

- they were received by the same patient,
- the dose levels match,
- one dose is from the subject diary, the other is from the CRF, and
- the two recorded doses took place within 2 hours of each other. This is considered sufficient to not mistakenly flag morning & evening doses on a twice daily regimen as duplicates but allows for inaccuracy in entering the exact time in the diary by the patient.

In case of duplicates, the record from the subject diary will be flagged. Flagged dosing entries will be excluded from summary statistics.

Any modifications to this identification procedure for duplicated dosing entries will be described in detail in the CSR.

### 6.3.15 Safety and Tolerability Analysis

The analysis of the safety variables will be based on the ITIFAS set.

#### 6.3.15.1 Adverse Events

All AEs will be listed including the items mentioned in Section 6.1.6.1 (except whether autopsy was performed). Additional listings will be produced for the following:

- Serious AEs
- Serious AEs leading to death

- AEs leading to discontinuation

In addition, the following summaries will be presented:

- Overall summary, displaying the number of:
  - TEAEs (overall, regardless of seriousness)
  - Serious AEs
  - Serious TEAEs
  - Non serious TEAEs
  - Related TEAEs
  - Severity of AEs
  - AEs leading to discontinuation
  - AEs leading to death
- TEAEs by SOC and PT
- Serious AEs by Severity, SOC and PT (including pre-treatment SAEs shown as a separate period)
- Non-serious TEAEs by Severity, SOC and PT
- Non-serious TEAEs by Relationship, SOC and PT
- Serious TEAEs by Relationship, SOC and PT

The overall summary and the summary of TEAEs by SOC and PT will display AEs by period using columns for the different periods. All other AE summaries will also be by period but will be split into multiple parts by period.

#### 6.3.15.2 Clinical Safety Laboratory Tests (Hematology, Blood Chemistry and Urinalysis)

As described in Section 6.1.6.2 only abnormal clinically significant laboratory results will be recorded. The abnormal laboratory results (hematology, blood chemistry and urinalysis) will be listed by patient and date. Abnormally high values will be flagged with 'H' and abnormally low values will be flagged with "L".

#### 6.3.15.3 Vital Signs

Vital signs data will be listed by patient, including period, visit, date, time and results.

Vital signs will also be summarized descriptively by period and visit.

#### 6.3.15.4 Physical Examination

The results of the physical examination will be listed by patient and time-point.

# 7. REFERENCES

1. SAS® Version 9.3 of the SAS System for Personal Computers. Copyright © 2011. SAS Institute Inc. SAS and all other SAS Institute Inc. product or service names are registered trademarks or trademarks of SAS Institute Inc., Cary, NC, USA.
2. WinNonlin Professional Software Version 6.3. http://www.pharsight.com

# 8. TABLES AND LISTINGS TO BE INCLUDED IN SECTION 14 OF THE CLINICAL STUDY REPORT

**Patient Disposition**

**Table 14.1.1.1** Patient Disposition (ITIFAS)

**Baseline and Demographic Data**

**Table 14.1.2.1** Summary of Patient Demographics (ITIFAS)

**Medical History**

**Table 14.1.3.1** Summary of Haemophilia History by Severity and Family History (ITIFAS)

**Table 14.1.3.2** Summary of FVIII and Bypassing Agent Treatments up to 12 Months Prior to Baseline Visit by Product Type and Product (ITIFAS)

**Table 14.1.3.3** Summary of Inhibitor History (ITIFAS)

**Table 14.1.3.4** Summary of Previous Inhibitor Treatments up to the Screening Visit (ITIFAS)

**Table 14.1.3.5** Summary of Allergy History by Product and Type of Reaction (ITIFAS)

**Table 14.1.3.6** Summary of Bleeding History by Location, Cause and Treatment up to 12 Months Prior to Baseline Visit (ITIFAS)

**Table 14.1.3.7** Summary of Blood Groups and Genotyping (ITIFAS)

**Concomitant Medication**

**Table 14.1.4.1** Summary of Concomitant Medication (ITIFAS)

**Treatment Adherence**

**Table 14.1.5.1** Summary of rFVIIIFc Treatment Adherence (ITIFAS)

**Treatment Outcome**

**Table 14.2.1.1** Analysis of ITI Outcome (ITIFAS)

**Table 14.2.1.2** Analysis of Prognostic Factors for ITI Outcome (ITIFAS)

**Table 14.2.1.3** Descriptive Analysis of Time to ITI Success Criteria Met (ITIFAS)

**Table 14.2.1.4** Kaplan-Meier Analysis of Time to ITI Success (ITIFAS)

**Table 14.2.1.5** Kaplan-Meier Analysis of Time to Confirmed Negative Titer (ITIFAS)

**Table 14.2.1.6** Kaplan-Meier Analysis of Time to Confirmed Incremental Recovery Greater Than Two Thirds of the Expected and Time to Confirmed Half-life >7 hours (ITIFAS)

**Table 14.2.1.7** Summary of Relapse (TPFAS)

**Table 14.2.1.8** Descriptive Analysis of Time to Relapse (TPFAS)

**Bleeding**

**Table 14.2.2.1** Summary of Bleeding During ITI Treatment (ITIFAS)

**Table 14.2.2.2** Summary of Annualized Bleeding Rate During 48-week Follow-up (TPFAS)

**Pharmacoeconomics**

# 9. FIGURES

# LISTINGS TO BE INCLUDED IN SECTION 16 OF THE CLINICAL STUDY REPORT

**Patient Disposition**

**Listing 16.2.1.1** Withdrawals from the Study (ITIFAS)

**Listing 16.2.1.2** Informed Consent (ITIFAS)

**Listing 16.2.1.3** Study Visits (ITIFAS)

**Listing 16.2.2.1** Time Window Deviations (ITIFAS)

**Listing 16.2.2.2** Protocol Deviations (ITIFAS)

**Listing 16.2.3.1** Assignment to Analysis Populations (ITIFAS)

**Baseline and Demographic Data**

**Listing 16.2.4.1** Patient Demographics (ITIFAS)

**Listing 16.2.4.2** Medical and Surgical History (ITIFAS)

**Listing 16.2.4.3** Haemophilia History (ITIFAS)

**Listing 16.2.4.4** Inhibitor History (ITIFAS)

**Listing 16.2.4.5** Bleeding History (ITIFAS)

**Listing 16.2.4.6** ITI History (ITIFAS)

**Listing 16.2.4.7** History of Allergy or Anaphylaxis Associated with any FVIII Product, rFVIIa, aPCC and Other Plasma Products (ITIFAS)

**Listing 16.2.4.8** HIV and Hepatitis Status (ITIFAS)

**Listing 16.2.4.9** Blood Group and FVIII Mutations (ITIFAS)

**Listing 16.2.4.10** HLA Class II Haplotypes (ITIFAS)

**Concomitant Medication and Procedures**

**Listing 16.2.5.1** Prior and Concomitant Medication (ITIFAS)

**Listing 16.2.5.2** Prior and Concomitant Procedures and Other Therapies (ITIFAS)

**Exposure and Adherence**

**Listing 16.2.6.1** Exposure to rFVIIIFc (ITIFAS)

**Listing 16.2.6.2** Exposure to Bypassing Agents (ITIFAS)

**Listing 16.2.6.3** Prescribed Treatment Regimens (ITIFAS)

**Listing 16.2.6.4** Treatment Adherence (ITIFAS)

**Listing 16.2.6.5** Prescribed Treatment Regimens (FUFAS)

**Inhibitor Titers and FVIII Activity**

**Listing 16.2.7.1** Inhibitor Titers (ITIFAS)

**Listing 16.2.7.2** FVIII:C (ITIFAS)

**Listing 16.2.7.3** Determinations of Incremental Recovery (ITIFAS)

**Listing 16.2.7.4** Determinations of FVIII Half-life (ITIFAS)

**Efficacy**

**Listing 16.2.8.1** Treatment Outcome (ITIFAS)

**Listing 16.2.8.2** Bleeding Episodes (ITIFAS)

**Listing 16.2.8.3** Total Number of Bleeding Episodes During ITI Treatment (ITIFAS)

**Listing 16.2.8.4** Bleeding Episodes and Rate During 48-week Follow-up Period (TPFAS)

**Pharmacoeconomics**

**Listing 16.2.9.1** Consumption of rFVIIIFc During the Study (ITIFAS)

**Listing 16.2.9.2** Consumption of rFVIIIFc and Bypassing Agents During the ITI Period (ITIFAS)

**Listing 16.2.9.3** Days Missed at School or Work (ITIFAS)

**Listing 16.2.9.4** Hospitalizations (ITIFAS)

**Safety Variables**

**Listing 16.2.10.1** All Adverse Events (ITIFAS)

**Listing 16.2.11.1** Vital Signs (ITIFAS)

**Listing 16.2.11.2** Physical Examination (ITIFAS)

# 11. DOCUMENTATION OF STATISTICAL METHODS

**Appendix 16.1.9.2.1** Statistical Analysis of Time to ITI Success/Success Criteria/Partial Success

# 12. APPENDICES

## 12.1 Schedule of Events

**Table 2 Schedule of events: Screening and ITI Period**

| Activities | Screening Visit - 4 weeks (- 2 weeks) from start of ITI treatment | ITI Period | | | |
|---|---|---|---|---|---|
| | | **Baseline Visit** | **Week 2 Visit** | **Interim ITI Visits** | **ITI Outcome Assessment Visit** |
| | | Start of ITI treatment | 2 weeks ±3 days) from start of ITI treatment | Every 4th week (±1 week ) starting at ITI Week 4 until negative titer (<0.6 BU/mL) is achieved OR 60 weeks of treatment | Every 4th week (±1 week) starting at time of first negative inhibitor titer until IR>66% of expected is achieved OR until 60 weeks of treatment. Every 2nd week (±3 days ) starting at time of first IR>66% until ITI success OR 60 weeks of treatment |
| Informed consent/assent | X | | | | |
| Assessment of patient eligibility | X | | | | |
| Demographics | X | | | | |
| Medical, surgical, haemophilia, inhibitor, bleeding and ITI history | X | | | | |
| Physical examination[a] | X | X | | X | X |
| Height | X | | | | |
| Weight (kg) | X | X | X | X | X |
| Vital signs[b] | X | X | X | X | X |
| Hematology[a] | X | X | | X | X |
| Blood chemistry[a] | X | X | | X | X |
| Urinalysis[a] | X | X | | X | X |
| Viral analysis[c] | X | | | | |
| Analysis of FVIII mutation[d] | | X | | | |
| HLA allotyping[d] | | X | | | |

| Activities | Screening Visit - 4 weeks (- 2 weeks) from start of ITI treatment | ITI Period | | | |
|---|---|---|---|---|---|
| | | Baseline Visit | Week 2 Visit | Interim ITI Visits | ITI Outcome Assessment Visit |
| | | Start of ITI treatment | 2 weeks ±3 days) from start of ITI treatment | Every 4th week (±1 week ) starting at ITI Week 4 until negative titer (<0.6 BU/mL) is achieved OR 60 weeks of treatment | Every 4th week (±1 week) starting at time of first negative inhibitor titer until IR>66% of expected is achieved OR until 60 weeks of treatment. Every 2nd week (±3 days ) starting at time of first IR>66% until ITI success OR 60 weeks of treatment |
| rFVIIIFc dosing[e] | | X | X | X | X |
| Nijmegen-modified Bethesda assay (inhibitor assay) | X | X | X | X | X |
| Exploratory anti-FVIII antibody | X | X | X | X | X |
| Exploratory blood sample for immune cell characterization[f] | | X | X | | |
| FVIII:C[g] | | X | X | X | X |
| FVIII:C for incremental recovery[h] | | | | | X |
| FVIII:C for half-life evaluation[i] | | | | | X |
| Diary review, including review of bleedings and rFVIIIFc dosing accountability[j] | | X | X | X | X |
| Non-serious adverse events | | X | X | X | X |
| Serious adverse events | X | X | X | X | X |
| Concomitant therapy/procedures | X | X | X | X | X |

[a] Every 12th week from the start of the ITI treatment period.

[b] Vital signs include blood pressure, pulse rate, respiratory rate, and temperature. Postdose assessments following rFVIIIFc injections should be taken approximately 20 minutes after the end of the injection.

[c] Sample to be used to determine seropositivity, including anti-HIV-1 and -2, anti-HBs, and anti-HCV, at screening, should patients be diagnosed with

HIV, hepatitis B, or hepatitis C, and results not already available in medical records.

[d] Not mandatory. To be collected at the baseline visit or at later visits unless results are available in medical records.

[e] Patients will be instructed that they will receive their daily dose of rFVIIIFc during the study visit after the samples for inhibitor testing and the FVIII:C pre-dose assessment are taken.

[f] A whole blood sample will be collected at the baseline visit (predose) and at Week 2, as allowable based on patient weight, regulatory guidelines and institutional practice regarding blood draw restrictions for pediatric patients.

[g] A pre-dose sample for FVIII:C will be collected at visits where samples for IR or t½ assessments are not collected.

[h] Assessment of incremental recovery will only be performed after negative inhibitor has been confirmed at two consecutive visits.

[i] Half-life determination will only be performed after incremental recovery >66% of the expected IR has been confirmed at two consecutive visits. Half-life determinations are to be performed after at least a 24-hour washout.

[j] It is recommended that patients/caregivers enter dosing information immediately after an injection.

**Table 3 Schedule of events: Tapering and follow-up period**

| Activities | Tapering period | Follow-up period | | Final safety follow-up |
|---|---|---|---|---|
| | **Tapering initiation visit, Week 2, 4, 8, 12 and 16 visits** | **Week 28 and 40 visits** | **End of treatment visit [a]** | **Final safety follow-up visit** |
| | Starting at ITI success and continuing for 16 weeks with visits after 2 weeks (±3 days), 4 weeks (±1 week) and then every 4th week (±1 week) | Visits week 28 and 40 (± 2 weeks) following ITI Success | Visit week 48 (± 2 weeks) following ITI Success OR 2 weeks (±3 days) after failure or 60 weeks of treatment | 7 to 14 days after the last dose of rFVIIIFc |
| Physical examination | X[b] | X | X | |
| Height | | | X | |
| Weight (kg) | X | X | X | |
| Vital signs[c] | X | X | X | |
| Hematology [d] | X | | X | |
| Blood chemistry [d] | X | | X | |
| Urinalysis [d] | X | | X | |
| rFVIIIFc dosing[e] | X | X | X | |
| Nijmegen-modified Bethesda assay (inhibitor assay)[f] | X | X | X | |

| Activities | Tapering period | Follow-up period | | Final safety follow-up |
|---|---|---|---|---|
| | **Tapering initiation visit, Week 2, 4, 8, 12 and 16 visits** | **Week 28 and 40 visits** | **End of treatment visit [a]** | **Final safety follow-up visit** |
| | Starting at ITI success and continuing for 16 weeks with visits after 2 weeks (±3 days), 4 weeks (±1 week) and then every 4th week (±1 week) | Visits week 28 and 40 (± 2 weeks) following ITI Success | Visit week 48 (± 2 weeks) following ITI Success OR 2 weeks (±3 days) after failure or 60 weeks of treatment | 7 to 14 days after the last dose of rFVIIIFc |
| Exploratory anti-FVIII antibody | X | X | X | |
| Exploratory blood sample for immune cell characterization[g] | X | | X | |
| FVIII:C for incremental recovery | X | X | X | |
| FVIII:C for half-life evaluation[h] | | | X | |
| Diary review, including review of bleedings and rFVIIIFc dosing accountability[i] | X | X | X | |
| Non-serious adverse events | X | X | X | X |

| Activities | Tapering period | Follow-up period | | Final safety follow-up |
|---|---|---|---|---|
| | **Tapering initiation visit, Week 2, 4, 8, 12 and 16 visits** | **Week 28 and 40 visits** | **End of treatment visit [a]** | **Final safety follow-up visit** |
| | Starting at ITI success and continuing for 16 weeks with visits after 2 weeks (±3 days), 4 weeks (±1 week) and then every 4th week (±1 week) | Visits week 28 and 40 (± 2 weeks) following ITI Success | Visit week 48 (± 2 weeks) following ITI Success OR 2 weeks (±3 days) after failure or 60 weeks of treatment | 7 to 14 days after the last dose of rFVIIIFc |
| Serious adverse events | X | X | X | X |
| Concomitant therapy/ procedures recording | X | X | X | X |

[a] Patients who do not achieve ITI success within 15 months will proceed to the end to treatment visit. Patients who develop inhibitors during the tapering or the follow-up period (i.e., who relapse) will proceed immediately to the end of treatment visit.

[b] Every 12th week during the tapering period.

[c] Vital signs include blood pressure, pulse rate, respiratory rate, and temperature. Postdose assessments following injections should be taken approximately 20 minutes after the end of the rFVIIIFc injection.

[d] During the tapering period, samples should be drawn every 12th week for testing.

[e] Patients will be instructed that they will receive their daily dose of rFVIIIFc during the study visit after the samples for inhibitor testing and the FVIII:C pre-dose assessment are taken.

[f] An unscheduled visit may be required to repeat inhibitor testing under this protocol in order to obtain a sample to confirm a positive inhibitor test result.

[g] If ITI success is declared, a sample will be collected at the first visit in the tapering period and at the end of the tapering period. If partial success or failure is declared a sample will be collected at the end of treatment visit.

[h] PK assessments for half-life determination are to be performed in patients with a low or negative titer after at least a 24-hour washout.

[i] It is recommended that patient/caregivers enter dosing information immediately after an injection.