Clinical Study Protocol
NCT03103542

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 3,0, Amended Protocol including Amendment 2
Sobi.Elocta-003

EudraCTno. 2017-000065-73

Type of Study: **Therapeutic Use, Phase IV**

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Investigator statement

I have read the protocol entitled "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" and the accompanying current summary of product characteristics. I agree to conduct the clinical investigation in compliance with the Amended protocol, Version 3.0, 26 February 2018, Council for Harmonisation (ICH) harmonised guideline E6(R2): Guideline for Good Clinical Practice (GCP) [1], applicable regulatory/government regulations, and in accordance with the ethical principles that have their origin in the Declaration of Helsinki [2].I will not implement any changes to study procedures or conduct without prior approval from the sponsor and, when applicable, the Independent Ethics Committee/Institutional Review Board and Regulatory Authority.

I agree to maintain the confidentiality of this study protocol, as described on the title page. Further, I will not publish results of the study without authorization from Swedish Orphan Biovitrum AB (publ).

Signature of Principal Investigator	Date
Printed Name of Principal Investigator	

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1 Synopsis

STUDY IDENTIFIERS	
Title of study:	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
Clinical study number:	Sobi.Elocta-003
Investigator(s):	Physician experienced in the treatment of haemophilia
Study center(s):	Approximately 20 Haemophilia Treatment Centres (HTC) or Comprehensive Care Centres (CCC) in Europe and North America
Type of study:	Therapeutic use, Phase IV
STUDY OBJECTIVES	
Primary objective:	To describe the outcome of ITI treatment performed with rFVIIIFc within a timeframe of 60 weeks in patients who failed previous attempts at tolerization including use of immunosuppressants
Secondary objective(s):	To describe time to tolerization 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.
Exploratory objective(s)	To explore the mechanism of ITI in patients undergoing ITI performed with rFVIIIFc.
STUDY ENDPOINTS	
Primary endpoint:	ITI success defined as achieving all 3 of the following criteria: • Negative titer for inhibitor (<0.6 BU/mL by the Nijmegen-modified Bethesda assay) at 2 consecutive visits • FVIII incremental recovery (IR) >66% of the expected IR at 2 consecutive visits • FVIII elimination half-life (t½) ≥7 hours

Secondary endpoint(s):	Time to ITI success Occurrence of relapse during a 48-week period following successful ITI treatment Number of bleedings during ITI treatment Bleeding rate during a 48-week period following successful ITI treatment Adverse events Consumption of rFVIIIFc Number of days missed school or work during ITI treatment Number of days missed school or work during a 48-week period following successful ITI treatment Number of hospitalizations during ITI treatment Number of hospitalizations during a 48-week period following successful ITI treatment Adherence
Exploratory endpoint(s):	Presence of FVIII specific anti-drug antibodies (ADA) Characterization of found ADA including subclass and isotype distribution, FVIII binding affinities and FVIII domain specificities Characterization of immune status including T-cell responses to rFVIIIFc

STUDY DESIGN AND METHODS

Study design:

This is an open-label, single-arm, interventional multi-center study designed to explore ITI performed with recombinant coagulation factor VIII Fc fusion protein (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 period indicating a stagnation in the tolerization attempt.

The study consists of four periods, a screening period, an ITI treatment period, a tapering period and a follow-up period.

Screening period

The screening period is 4 to 6 weeks. During screening, patients will continue their current treatment regimen in accordance with the local standard of care. Patients who meet all inclusion and no exclusion criteria will be enrolled into the study.

ITI period

All patients will receive rFVIIIFc 200 IU/kg daily until successful tolerization or failure or for a maximum period of 60 weeks. Inhibitor titers and FVIII activity (FVIII:C) will be assessed locally at each visit. If FVIII:C levels raise above 200 IU/dL during the ITI period, the dose should be adjusted according to investigator judgment to maintain the peak FVIII:C levels between 100-200 IU/dL.

If, after the initial 3 months, a downward trend of at least 20% in the inhibitor titer in a 6-month period is not seen, the patients should be regarded as a treatment failure and complete the end of treatment visit as soon as possible.

Patients may achieve 1 of 4 outcomes: ITI success, partial success, treatment failure or not determinable due to withdrawal during the ITI period.

ITI success is defined as achieving all 3 of the following criteria in the following order 1, 2 and 3:

1. Negative titer for inhibitor (<0.6 BU/mL by the Nijmegen-modified Bethesda assay) in 2 consecutive determinations
2. Incremental recovery (IR) > 66% of the expected IR, in 2 consecutive determinations.
3. Elimination half-life (t½) ≥7 hours

A patient who achieves ITI success within 60 weeks continues into the tapering period. A patients who achieves partial ITI success or failure will not continue into the tapering period but conduct the end of study visit.

Tapering period

During the tapering period the dose will be reduced with the aim to reach prophylactic dose after a total of 16 weeks. The dose and regimen will be adjusted by the investigator in accordance with local practice and investigator judgment. The length of the tapering period can be adjusted after approval by the sponsor medical director. Inhibitor titers and FVIII:C will be assessed locally at each visit. During the tapering period patients will be monitored for relapse.

Relapse is defined as the occurrence of the following (with or without clinical signs or symptoms) after complete ITI success:

• A positive inhibitor (≥0.6 BU using the Nijmegen assay) on 2 consecutive assessments, performed within 2-4 weeks

and

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

Any patients with relapse will conduct the end of study visit directly.

Follow-up period

During the follow-up period patients will be treated prophylactically with dose and frequency prescribed by the investigator, according to the label and clinical response of the patient, for 32 weeks. Inhibitor titers and FVIII:C will be assessed locally at each visit. During the follow-up period the patient will be monitored for relapse. Any patients with relapse will conduct the end of treatment visit directly. After the patient has completed the end of treatment visit, they should be treated and followed-up according to investigator judgment and local practice and no further investigational medicinal product will be provided. A final safety follow-up call or visit will be conducted 1-2 weeks after the end of treatment visit.

Number of patients planned:	20 patients receiving at least one dose of rFVIIIFc

Diagnosis and main criteria for inclusion:	Male patients of any age diagnosed with severe haemophilia A Previously treated with any plasma-derived or recombinant conventional or extended half-life FVIII Diagnosed with high titer inhibitors (historical peak ≥5 BU/mL according to medical records) Inhibitor titer ≥0.6 BU at screening Documented failed previous ITI attempt(s)
Assessments:	Lab samples will be drawn for assessment of inhibitor titer and rFVIIIFc activity. Samples will be analyzed both locally and at a central laboratory. The results from the local laboratory will constitute the primary data of the study to be used for statistical analysis and clinical decision making. Occurrence of bleeds (spontaneous and traumatic) and associated details will be collected through a patient diary. Serious adverse events will be collected from informed consent until the safety follow-up visit. Adverse events will be collected from the baseline visit until the safety-follow-up visit. Clinical significant abnormal lab values as assessed by the investigator will be reported as AEs and the associated value (local laboratory) will also be collected. rFVIIIFc consumption, days missed from school or work and hospitalizations will be collected for health economic assessments.
Test product; dose and mode of administration:	In Europe and Canada, rFVIIIFc will be supplied as rFVIIIFc powder and solvent for solution for intravenous injection in different vial strengths. The manufacturing of drug substance and drug product for the clinical study will not differ from the manufacturing of commercial available ELOCTA®. Drug product will be packaged and labeled for clinical trial use. In USA, commercial available ELOCTATE® in different vial strengths, with additional labeling for clinical trial use, will be used as rFVIIIFc supply. Dose ITI period: 200 IU/kg/day which may be given as once daily doses, or divided in two doses per day. Dose tapering period: The dose and regimen will be adjusted by the investigator in accordance with local practice and investigator judgment. Dose follow-up period: Prophylactic dose decided by the investigator according to the label and clinical response of the patient.
Reference product; dose and mode of administration:	Not Applicable
Duration of treatment(s):	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+ 2 weeks of safety follow-up.
Statistical methods:	Descriptive statistics will be used to summarize the outcomes in the study and no inferential statistics will be performed. Time to ITI success will be analyzed using Kaplan-Maier method. The proportion of patients achieving ITI success and partial ITI success will be calculated. The proportion of patients relapsing after achieving successful tolerance will be calculated. The number of bleeds for the ITI period will be summarized descriptively. For each of the tapering and follow-up periods the annualized bleeding rate will be calculated and summarized descriptively. Safety data will be presented descriptively across the entire study as

well as by each period. Consumption will be calculated for the entire study as well as for each of the periods separately.

2 Abbreviations and definition of terms

aPCC	Activated Prothrombin Complex Concentrate
AE	Adverse event
ALT	Alanine aminotransferase
ADA	Anti Drug Antibody
AST	Aspartate aminotransferase
BDD	B-domain deleted
BU	Bethesta units
CD4	Cluster of differentiation 4
CDASH	Clinical Data Acquisition Standards Harmonization
CDISC	Clinical Data Interchange Standards Consortium
CL	Clearance
CRO	Contract research organization
CRF	Case report form
ECG	Electrocardiogram
EOT	End Of Treatment
FVIII:C	Factor VIII activity
FUFAS	Follow up full analysis set
GCP	Good clinical practice
GLP	Good laboratory practice
HCV	Hepatitis C virus
HEK	Human embryonic kidney
HIV	Human Immunodeficiency Virus
HLA	Human Leukocyte Antigen
IgG	Immunoglobulin G
ICF	Informed consent form
IEC	Independent Ethics Committee
IR	Incremental recovery
IRB	Institutional Review Board
ITI	Immune Tolerance Induction

ITIFAS	ITI full analysis set
MedDRA	Medical Dictionary for Regulatory Activities
NCA	Non Compartmental Analysis
pdFVIII	Plasma-derived FVIII
PK	Pharmacokinetics
PUP	Previously Untreated Patient
QOL	Quality Of Life
rFVIIIFc	Recombinant Coagulation Factor VIII Fc Fusion Protein
SAE	Serious adverse event
SAP	Statistical Analysis Plan
Sobi	Swedish Orphan Biovitrum
SUSAR	Suspected Unexpected Serious Adverse Reactions
SDTM	Study Data Tabulation Model
$t_{1/2}$	Elimination half-life
TPFAS	Tapering phase full analysis set
ULN	Upper Limit of Normal
UK NEQAS	United Kingdom National External Quality Assessment Service
V_{SS}	Volume of distribution at Steady-State

3 Ethics

3.1 Independent ethics committee

It is the responsibility of the investigator to obtain approval of the study protocol, possible amendments and the written patient information and informed consent form (ICF) from the Independent Ethics Committee (IEC)/Institutional Review Board (IRB). The investigator should file all correspondence with the IEC/IRB. Copies of IEC/IRB correspondence and approvals should be forwarded to the contract research organization (CRO).

3.2 Ethical conduct of the study

This study will be conducted in compliance with this protocol, the International Conference on Harmonization (ICH) Guideline for Good Clinical Practice (GCP) [1], applicable regulatory

requirements, and in accordance with the latest revision of the Ethical Principles for Medical Research Involving Human Subjects (the Declaration of Helsinki) [2].

3.3 Patient information and consent

It is the responsibility of the investigator to give each patient and/or the patient's legally authorized representative prior to any study related activities, full and adequate verbal and written information regarding the objective and procedures of the study and the possible risks involved. The patients and/or the patient's legally authorized representative must be informed about their right to withdraw from the study at any time without prejudice. The patient and/or the patient's legally authorized representative(s), may be provided with the informed consent document(s) prior to the screening visit to allow adequate time for review and an opportunity to discuss the study with the investigator/designee. After reviewing, the patient and/or the patient's legally authorized representative will come into the clinic to sign the informed consent. This consent must be dated and retained by the investigator as part of the study records. The term of the consent and when it was obtained must also be documented in the CRF system.

The written patient information and/or consent form must not be changed without prior discussion with Sobi. If a protocol amendment is required, the informed consent form may need to be revised to reflect the changes to the protocol. Before any revisions are implemented, the revised written patient information and/or consent form must be approved by the IEC/IRB, and signed by all patients subsequently enrolled in the study as well as those currently enrolled in the study.

It is the responsibility of the investigator to obtain signed informed consent from all patients and/or the patient's legally authorized representative prior to any study related activities. Assent should be obtained from pediatric patients according to local requirements. The patients or the patient's legally authorized representative should receive a copy of the written information and signed informed consent form and, if applicable, assent form.

4 Study administrative structure

4.1 Sponsor

The sponsor of the study is Swedish Orphan Biovitrum AB (publ), Stockholm, Sweden.

4.2 Collaborator

This study is designed and financed by Sobi and Bioverativ as part of their collaboration agreement.

4.3 Contract research organization

A CRO, PAREXEL International (IRL) Limited, 70 Sir John Rogerson's Quay, Dublin, Ireland will be responsible for administrative aspects of the study including, but not limited to, study initiation, monitoring, and management of SAE reports and data management. Before patients are screened at each study site, the CRO will review study responsibilities with the investigators and other study site staff, as appropriate.

The CRO will assign a vendor to provide and manage electronic diaries.

4.4 Laboratories

Coagulation factor VIII (FVIII) inhibitor titer, FVIII activity (FVIII:C) and safety laboratory samples will be collected and analyzed at the local laboratory of each center. If the local laboratory is not able to provide the required laboratory tests, another local or national qualified laboratory may perform the analyses.

Central laboratories have also been selected by Sobi to analyze the FVIII inhibitor titer, FVIII:C, FVIII anti-drug antibodies (ADA), human leukocyte antigen (HLA) allotyping, FVIII mutation and the exploratory samples being collected in the study. Further details are provided in the laboratory manual.

5 Introduction

5.1 Background

5.1.1 Overview of immune tolerance induction in the clinical management of haemophilia A

Haemophilia A is an X-linked bleeding disorder that is caused by a functional deficiency of FVIII, a cofactor in the intrinsic coagulation pathway. Haemophilia A is categorized based on endogenous FVIII activity levels as severe (<1 IU/dL), moderate (1 to 5 IU/dL), and mild (>5 to <40 IU/dL) [3,4,5]. As there yet is no available cure for haemophilia A, current treatment focuses on replacement therapy with clotting factor concentrates, namely plasma-derived FVIII (pdFVIII) or recombinant FVIII (rFVIII) products.

The formation of neutralizing anti-FVIII alloantibodies (inhibitors) represents the most serious complication related to haemophilia treatment [6]. Inhibitors are immunoglobulin G (IgG) antibodies formed against specific epitopes of the FVIII molecule, which can neutralize FVIII:C and reduce the recovery and half-life of FVIII. Approximately 30% of previously untreated patients (PUPs) with severe haemophilia A develop inhibitors following exposure to replacement FVIII [7,8]. The presence of inhibitors makes it more difficult to control bleeding because patients no longer respond to standard doses of replacement FVIII. As a result, patients with

inhibitors are prone to more bleeds which can lead to severe joint disease and physical disability and consequently reduced quality of life [9]. Inhibitor patients also have a higher mortality due to bleeding complications [10].

Inhibitors are classified as high-titer or low-titer based on the titer measured by the Bethesda assay. Low-titer inhibitors measure <5 BU/mL, are primarily transient (usually spontaneously resolve within 6 months but sometimes more slowly), and generally do not reappear upon FVIII challenge [11,12]. High-titer inhibitors are defined by a peak inhibitor titer ≥5 BU/mL and are usually persistent. While it has been reported that 10% of patients with a high-titer inhibitor (≥5 BU/mL) had a transient inhibitor that spontaneously resolved within 6 months [12], only 3.4% of patients with a very high-titer inhibitor (≥10 BU/mL) had an inhibitor that spontaneously resolved after at least 2 years of follow-up [11], suggesting that a titer of ≥10 BU/mL is a better predictor for a persistent inhibitor.

In patients with low-titer inhibitors, bleeding events may be controlled with increased doses of replacement FVIII to overwhelm the inhibitor by antigen excess. In patients with high-titer inhibitors, bleeding is treated with bypassing agents (such as activated prothrombin complex concentrate [aPCC] or recombinant activated FVII [rFVIIa]), which can bypass FVIII inhibition.

The goal of ITI is to tolerize the immune system to FVIII by regular antigen exposure and to restore FVIII pharmacokinetics (PK) such that replacement of FVIII can be reintroduced at standard doses. A successful response to an ITI regimen (i.e. immune tolerance) is based on evaluation of inhibitor titer, FVIII recovery, FVIII half-life, and elimination of the anamnestic response to FVIII challenge [6, 13].

Over the last 30 years, multiple ITI regimens have been developed. All involve frequent, often daily, exposure to FVIII continuing for months or years. ITI regimens employ different FVIII doses and dosing frequencies, and may involve adjunctive immunomodulatory therapy [13,14]. Currently, a range of FVIII products and dosing regimens are used for ITI because there is no clear consensus on an optimal regimen [14]. In the only prospective randomized dose comparison ITI study (International ITI Study), the time to ITI success was shorter and there were fewer bleeding events with a high-dose, more frequent ITI regimen (200 IU/kg daily) than a low-dose, less frequent ITI regimen (50 IU/kg 3 times per week) [15].

ITI success rates range from 33% to 88% in published studies [15,16,17,18,19,20,21,22,23,24]. Definitions of success and methods for calculating success rates differ across ITI studies. Numerous factors have been suggested to influence the wide variability in success rates, including differences in FVIII product types and dosing regimens and patient characteristics. In particular, historical peak inhibitor titer >200 BU/mL, inhibitor titer at ITI start ≥10 BU/mL, age at ITI start ≥8 years, time between inhibitor diagnosis and ITI start >2 years, and previous ITI failure have been correlated with decreased ITI success and are considered high-risk factors for poor ITI outcome [13,15,18,21].

Patients who have failed ITI can be exposed to additional ITI attempts, or “Rescue ITI”. Previous ITI failure(s) confer these patients a high risk of not succeeding with additional ITI attempts. There is limited data on the success rate and time to tolerance of Rescue ITI and on the criteria that influence the probability of success in rescue ITI treatments [21].

5.1.2 Previous non-clinical and clinical experience with rFVIIIFc for immune tolerance induction

Recombinant coagulation factor VIII Fc fusion protein (rFVIIIFc) is produced in a human cell line (HEK293) as a recombinant B-domain deleted (BDD) factor VIII fused to the Fc domain of human IgG. HEK-produced proteins have the same post-translational modifications as native human proteins, in contrast to proteins produced in cell lines from other species, such as hamsters (e.g. Chinese hamster ovary [CHO] cells). In such proteins, non-human glycans (such as N-glycolylneuraminic acid, NGNA) resulting from the post-translational modifications, can be potentially immunogenic. NGNA is not found in rFVIIIFc.

Until recently, all rFVIII products were produced in hamster cells (Baby Hamster Kidney (BHK) or CHO cells). Today, in addition to rFVIIIFc there is only one recently approved rFVIII product produced in a human cell line available on the market [25].

Nonclinical studies have shown that fusion proteins containing IgG or the Fc domain can induce tolerance to the A2 and C2 domains of the FVIII molecule, which are the most frequent epitopes targeted by inhibitors. In one study, FVIII-deficient mice were treated with B-cells expressing full-length IgG fused to either the A2 or C2 domain [26]. Inhibitor titers were significantly reduced in animals treated with a combination of B-cells expressing the A2-IgG and C2-IgG fusion proteins compared with control animals. In another study, a fusion protein comprising Fc and either the A2 or C2 domain was transplacentally delivered to the progeny of FVIII-deficient (HemA) pregnant mice [27]. The combination of A2Fc and C2Fc fusion proteins led to a significant reduction in inhibitor titers in the offspring of treated mother mice compared with the offspring of control mother mice. In both studies, the tolerogenic effect of the fusion proteins involved the induction of regulatory T-cells.

In line with the above findings that suggest a role of the Fc domain in tolerance, nonclinical data suggest that rFVIIIFc as such can induce tolerance to FVIII. In a nonclinical study, FVIII-deficient mice that were pretreated with rFVIIIFc had reduced total anti-FVIII IgG antibody and FVIII inhibitor production upon challenge with a high dose of rFVIIIFc [28]. Tolerance induced by rFVIIIFc was associated with a higher percentage of regulatory T-cells, a lower percentage of pro-inflammatory T-cells in the spleen, and upregulation of cytokines associated with attenuation of the immune response.

rFVIIIFc has been approved for the treatment of haemophilia A in the USA and Canada in 2014 with the name of ELOCTATE® and in Europe in 2015 with the name of Elocta®.

In the clinical setting, there are published case reports of patients who have received rFVIIIFc for ITI. Malec and coworkers describe three patients with severe haemophilia A (age at initiation of ITI was 18 months, 7.5 years and 10 years) who were started on ITI with rFVIIIFc after detection of a high-titer inhibitor. ITI was initiated at a dose of 100–200 IU/kg rFVIIIFc with a dosing interval of every other day to three times weekly. ITI led to a negative inhibitor in all 3 children within 4 to 12 weeks [29], which is shorter than the median time to negative inhibitor reported for other FVIII products [15,21]. In a recent poster presentation at ASH Ragni and coworkers reported the time to tolerance in the 3 cases being 17 weeks, 18 weeks and 17 months. After a follow-up period of 18-19 months, two of the three patients still had negative inhibitor

titers, whereas one of the three patients had a relapse of a low-titer inhibitor of 0.8 BU after weaning of the rFVIIIFc dosing to 80 IU/kg 3 times weekly [30]. Groomes and coworkers reported a 15 months old patient who started ITI on conventional rFVIII products. As the inhibitor titer continued to increase he was switched to rFVIIIFc 50 IU/kg thrice weekly. The inhibitor titer had significantly decreased to 0.7 BU/mL after 10 months of ITI at the time of publication [31]. In a retrospective chart review by Carcao and coworkers of 12 patients undergoing rescue ITI with rFVIIIFc 7 patients became Bethesda titer negative. Median time to attain a negative titre was 14.1 weeks (range 3-67.6 weeks). Three of these patients also achieved normal FVIII recovery at 3, 14 and 65 weeks and a fourth patient reached normal FVIII half-life at 27 weeks [32].

5.2 Study rationale

Current ITI regimens with conventional FVIII products usually require a long ITI treatment period with very high FVIII doses to achieve tolerance [15,17,33,34,35,36]. ITI success rates of 53-79% have been reported [15]. Patients who failed previous ITI attempts may be more difficult to tolerize with additional ITI attempts. There is therefore an unmet need to improve ITI treatment. As there is non-clinical evidence on immune modulatory effects of rFVIIIFc and spontaneously reported clinical ITI cases indicating potential benefits of rFVIIIFc in ITI as compared to conventional FVIII products, it is of interest to describe the outcome of ITI treatment performed with rFVIIIFc in patients who failed previous attempts.

5.3 Potential risks and benefits

The benefit of giving rFVIIIFc to these patients is the potential to induce tolerance, i.e. eradicate the inhibitor. In patients that become tolerant, rFVIIIFc can provide prevention and treatment of bleeds.

Sustained high FVIII:C levels in plasma >150-200 IU/kg over a longer period of time may increase the risk of thrombotic side effects, although this risk is known to be low. Therefore, FVIII:C levels in plasma will be monitored in order to provide a basis for adjustment of the rFVIIIFc dose when needed. The dose planned for ITI in this study (200 IU/kg/day) is the established high dose ITI treatment schedule. As long as the inhibitor is present, all or most of the administered rFVIIIFc will be neutralized by the inhibitor shortly after administration, even if large rFVIIIFc doses are given. Tapering of the rFVIIIFc dose starts when the patient has fulfilled all three criteria for tolerance. However, already at a low-titer inhibitor (<5 BU/mL), and before all three tolerance criteria have been confirmed, the rFVIIIFc dose may be decreased if needed at the investigator's discretion in order to avoid very high FVIII:C levels in plasma.

As a precautionary measure, the first ITI dose will be administered at the hospital.

As pediatric patients may be included in the study, maximum blood sample volumes per visit and per month will be defined depending on body weight and in compliance with European Commission guidance [41]. If the maximum blood sample volume can be foreseen to be

exceeded at a visit or within a 4-week period, a predefined priority list will select which samples to draw.

6 Study objectives and endpoints

6.1 Primary objective

To describe the outcome of ITI treatment performed with rFVIIIFc within a timeframe of 60 weeks in patients who failed previous attempts at tolerization including use of immunosuppressants.

6.1.1 Primary endpoint

ITI success, defined as achieving all 3 of the following criteria:

- Negative titer for inhibitor (<0.6 BU/mL by the Nijmegen-modified Bethesda assay) at 2 consecutive visits
- FVIII incremental recovery (IR) >66% of the expected IR at 2 consecutive visits.
- FVIII elimination half-life (t½) ≥7 hours

6.2 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.

6.2.1 Secondary endpoints

Time to ITI success

Occurrence of relapse during a 48-week period following successful ITI treatment

Number of bleedings during ITI treatment

Bleeding rate during a 48-week period following successful ITI treatment

Adverse events

Consumption of rFVIIIFc

Number of days missed school or work during ITI treatment

Number of days missed school or work during a 48-week period following successful ITI treatment

Number of hospitalizations during ITI treatment

Number of hospitalizations during a 48-week period following successful ITI treatment

Adherence

6.3 Exploratory objectives

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

The exploratory objective will be reported in a separate report.

6.3.1 Exploratory endpoints

Presence of FVIII specific anti-drug antibodies (ADA)

Characterization of found ADA including subclass and isotype distribution, FVIII binding affinities and FVIII domain specificities

Characterization of immune status including T-cell responses to rFVIIIFc

7 Investigational plan

7.1 Overall study design and plan

This is an open-label, single-arm, interventional multi-center study designed to explore ITI treatment 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 must have undergone at least one failed ITI treatment attempt with the following characteristics:

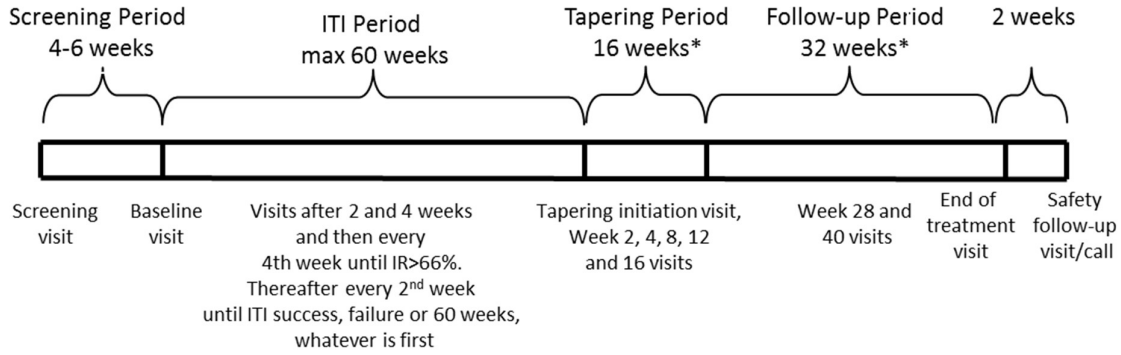
- A minimum FVIII dose equivalent to the low dose arm of the International ITI study (50 IU/kg, 3 times/week)
- A minimum ITI treatment period of 33 months or

- Shorter than 33 months if no downward trend of at least 20% in the inhibitor titer in any 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, receiving at least one dose, recruited from countries in Europe and in North America. The study consists of a 4 to 6 week 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.

7.1.1 Screening period

After informed consent is given by patient and/or his legally authorized representative, patients will undergo study specific procedures as per the schedule of events (Table 1, Table 2). During the 4- to 6-week screening period, patients will continue with their current treatment regimen in accordance with the local standard of care. Patients who meet all inclusion and no exclusion criteria will be enrolled into the study.

7.1.2 ITI period

The first dose of rFVIIIFc will be administered at the baseline visit and the ITI treatment will continue until ITI success or failure is declared, or for a maximum of 60 weeks. The ITI regimen

consists of daily administration of rFVIIIFc (200 IU/kg per day), which may be given as once daily injection or divided in two injections per day at the discretion of the investigator.

Visits will occur 2 and 4 weeks after the baseline visit and then every 4th week. For patients who achieves an IR >66% of the expected IR for each specific patient as per investigator judgment, the visit frequency will be changed to every other week.

During the ITI period patients will undergo procedures and assessments as per the schedule of events (Table 1). Samples for inhibitor testing and assessment of FVIII:C levels will be analyzed at the local laboratory as well as centrally. The results from the local laboratory will constitute the primary data of the study to be used for statistical analysis.

At each visit the inhibitor titer will be assessed. If, after the initial 3 months, a downward trend of at least 20% in the inhibitor titer in any 6-month period is not seen, the patients should be regarded as a treatment failure and complete the end of treatment visit as soon as possible.

The assessment of ITI outcome is illustrated in Figure 2. Once a patient has demonstrated negative inhibitor (<0.6 BU/mL) at two consecutive visits, evaluation of IR will be performed at the next visit. When an IR >66% of the expected IR has been obtained at 2 consecutive visits, pharmacokinetic assessments to determine half-life will be performed at the subsequent visits until a half-life of ≥7 hours is attained. Patients are required to have at least a 24-hour washout prior to the half-life assessment.

An unscheduled visit after the 60-week period may be scheduled to allow the patient to get a confirmatory test, as long as the first test occurred during the 60-week period. If the second test confirms the results of the first test, the date of ITI outcome is the date of the first value, which occurred during the 60-week period. Fluctuations in inhibitor levels is common and variability in inhibitor titer is expected. Patients will be evaluated on a case-by-case basis.

Throughout the study, FVIII:C levels above 200 IU/dL should be avoided. Therefore, based on the FVIII:C levels, already at a low-inhibitor titer (< 5 BU/mL), and before all three tolerance criteria have been confirmed, the rFVIIIFc dose may be decreased if needed at the investigator's discretion. Unscheduled sampling and visits may be performed to monitor the peak FVIII:C levels, according to investigator judgment.

During the ITI period, treatment of bleeding episodes will be according to investigator judgment and local practice. The use of bypassing agents such as aPCC and rFVIIa will be allowed but patients should be instructed to contact the investigator. Prescription of bypassing agents should be according to investigator´s judgment and local practice and if not in accordance with local label the medical monitor is to be notified and the rationale documented. The prophylactic prescription of bypassing agents requires notification by the investigator to the medical monitor and documentation of rationale. In patients with low-titer inhibitors (<5 BU/mL) and when rFVIIIFc can provide sufficient hemostatic control, as judged by the investigator, bypassing agents should be discontinued.

Throughout the ITI period administration of rFVIIIFc and any bypassing agents as well as any bleeding episodes will be registered by the patient and/or his caregiver in a study specific diary.

The diary data will be reviewed by the investigator on an ongoing basis and discussed with the patient at each visit.

ITI outcome

ITI outcome will be assessed on an ongoing basis. Patients may achieve 1 of 4 outcomes: ITI success, partial success, treatment failure or not determinable due to withdrawal during the ITI period.

ITI success

The following criteria (in order 1, 2 and 3) have to be fulfilled 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. Elimination half-life ($t_{½z}$) ≥ 7 hours

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

Partial success

Partial success is defined as achieving negative inhibitor titer and one of the pharmacokinetic parameters of ITI success: IR >66% OR elimination half-life ≥7 hours.

The determination of partial success will be made only among patients who have completed the maximum period of 60 weeks of ITI but do not fulfill the criteria for ITI success or treatment failure.

Treatment failure

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

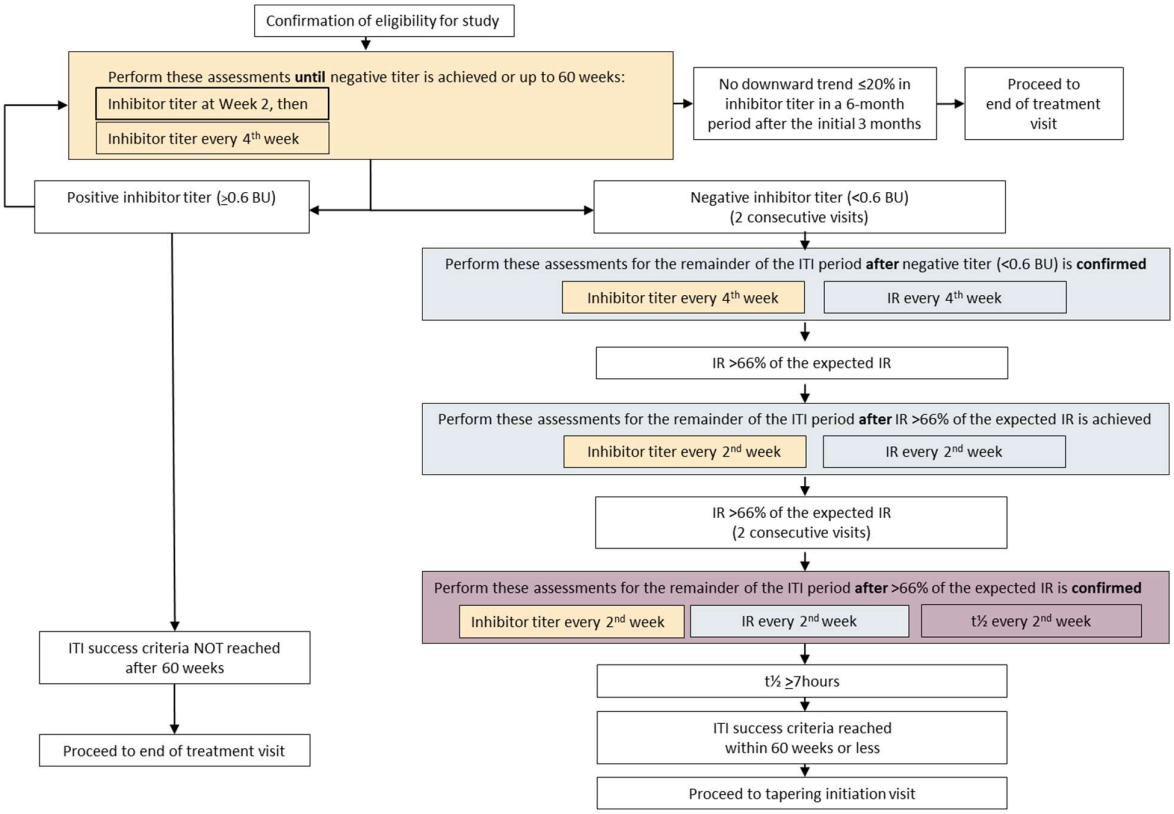
1. No downward trend of at least 20% in the inhibitor titers in any six (6) months after the initial three (3) months of ITI treatment
2. Presence of a sustained positive inhibitor (≥ 0.6 BU/mL) after 60 weeks of ITI
3. Negative inhibitor titer without either achieving IR > 66% of expected IR or Elimination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

Not determinable due to withdrawal during the ITI period

A patient should be withdrawn from the study treatment and discontinue the study for any one of the reasons described in Section 7.3.3.

Patients who achieve ITI success will enter the tapering period. For patients who achieve the outcome of partial success or treatment failure at the end of the ITI period or who are withdrawn, an end of treatment visit will be scheduled.

Figure 2 Flow diagram for assessment of ITI outcome



7.1.3 Tapering period

Patients who meet the criteria for ITI success will enter the tapering period.

Visits will occur 2 and 4 weeks after the first visit in the tapering period and then every 4th week during a total of 16 weeks. The duration of the tapering period may be modified by the investigator with the sponsor's medical director's approval based on the patient's clinical response. If the tapering period exceeds 16 weeks, an unscheduled visit should be performed every 4th week and at the end of the tapering period.

During this period the ITI dose of rFVIIIFc will be tapered down according to investigator judgment based on the FVIII:C results to maintain the peak FVIII:C levels between 100-200

IU/dL during the initial part of the tapering period, with an aim to taper the FVIII:C levels to reach prophylactic levels as judged by the investigator at the end of the tapering period. Further details about the recommended dosing regimen for tapering are described in Section 7.4.2 and in the pharmacy manual.

Bleeding episodes during the tapering period should be treated with rFVIIIFc, with doses according to investigator judgment and local practice. In specific situations, e.g. if bleeding is unresponsive to treatment with rFVIIIFc, treatment with bypassing agents may be considered as judged by the investigator. Such use is to be notified to the medical monitor and the rational documented in the medical records. Patients with bleedings during the tapering period is to be tested for recurrence of inhibitors.

During the tapering period, patients will undergo procedures and assessments as per the schedule of events (Table 2). At each visit samples for inhibitor titer and IR assessments will be drawn to monitor for relapse.

Relapse

Relapse is defined as the occurrence of the following (with or without clinical signs or symptoms) after complete ITI success, based on the International ITI criteria [15]:

- A positive inhibitor (≥0.6 BU using the Nijmegen assay) on 2 consecutive assessments, performed within 2-4 weeks

AND

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

If any assessments indicate relapse at any time during tapering or follow-up, the tests must be repeated at an unscheduled visit within 2 to 4 weeks to confirm relapse. A patient with confirmed relapse criteria will complete the end of treatment visit.

Throughout the tapering period all rFVIIIFc administration and any bleeding episodes will be registered by the patient and/or his caregiver in a study specific diary. The diary data will be reviewed by the investigator on an ongoing basis and discussed with the patient at each visit.

7.1.4 Follow-up period

After completion of the tapering period, patients will enter the follow-up period. During the follow-up period patients will be treated prophylactically for up to 32 weeks with dose and frequency prescribed by the investigator, and according to the label and clinical response of the patient. If the tapering period has been prolonged, the follow-up period should be shortened accordingly but should not be less than 24 weeks.

During the follow-up period patients will visit the clinic every 12 weeks and undergo procedures and assessments as per the schedule of events (Table 2). At each visit, samples for inhibitor titer and IR assessments will be drawn to monitor for relapse. A patient with confirmed relapse criteria will complete the end of treatment visit.

In order to avoid bleeds and a relapse of the inhibitor titer, FVIII:C levels should be kept ≥1 IU/dL. Bleeding episodes during the follow-up period should be treated with rFVIIIFc, with doses according to investigator judgment and local practice. In specific situations, e.g. if bleeding is unresponsive to treatment with rFVIIIFc, treatment with bypassing agents may be considered as judged by the investigator. Such use is to be notified to the medical monitor and the rational documented in the medical records. Patients with bleedings during the follow-up period is to be tested for recurrence of inhibitors.

At the end of treatment visit, pharmacokinetic assessments to determine IR and half-life, if deemed measurable based on pre-dose FVIII:C, will be performed. Patients are required to have at least a 24-hour washout period prior to the half-life assessment.

Throughout the follow-up period rFVIIIFc administration and any bleeding episodes will be registered by the patient and/or his caregiver in a study-specific diary. The diary data will be reviewed by the investigator on an ongoing basis and discussed with the patient at each visit.

After the patient has completed the end of treatment visit, they should be treated and followed-up according to investigator judgment and local practice. No further investigational medicinal product will be provided.

7.1.5 Safety follow-up

A final safety follow-up visit or telephone call will take place within 7 to 14 days after the end of treatment visit.

7.1.6 Unscheduled visits

Patients may return for an evaluation any time their condition warrants medical attention, or to repeat safety assessments, protocol-required assessments, including evaluations of inhibitor, pre-dose FVIII:C, IR, or PK, or any blood sampling, as necessary for study purposes. An unscheduled visit should not affect the regular visit schedule and assessments.

7.2 Discussion of study design

7.2.1 Discussion of design

The trial design is based on the International ITI study [15] and is aligned with the high-dose Bonn protocol [37]. This design was chosen as it is the ITI treatment design for which there is most experience [21].

60 weeks duration of ITI treatment was chosen as it is longer than the median time to complete success in the International ITI study, but shorter than the maximum range, as there are data indicating a relatively short time to tolerance when ITI is performed with rFVIIIFc [38].

The tapering period of 16 weeks is included in order to allow for a successive dose reduction, as a fast dose reduction may increase the risk of relapse.

The patient is monitored for 32 weeks during the follow-up period to check for a recurrence of inhibitors.

7.2.2 Discussion of dose

The proposed dose of rFVIIIFc for ITI (200 IU/kg/day) in this study is aligned with current ITI practice and guidelines [13,15,37]. Results from the International ITI study [15] which only included patients with a low risk of ITI failure demonstrated that the time to achieve negative inhibitor titer, normal FVIII incremental recovery, and FVIII tolerance respectively was shorter in patients treated with the high dose of FVIII (200 IU/kg/day), compared to patients treated with the low dose (50 IU/kg/3 times per week). Furthermore, patients treated with the high dose for ITI had a lower rate of intercurrent bleeding and fewer hospitalizations due to bleeding than patients treated with the low dose. A recent publication presented data on ITI treatment with a plasma derived von Willebrand factor containing FVIII product in 48 prospectively treated patients with low risk and high risk for ITI failure using similar doses. At ITI start, low risk patients received 50–100 IU FVIII/kg daily, or every other day, and high risk patients received 100 IU FVIII/kg every 12 h [21].

No dose-limiting toxicities (DLT) were observed in the nonclinical animal studies where repeated doses of up to 1000 IU/kg were evaluated. Daily injections of rFVIIIFc 200 IU/kg will be allowed in the ITI regimen, since exposure is expected to be much lower in patients undergoing ITI in the presence of inhibitors [15].

The suggested tapering strategy is similar to that used on the International ITI Study protocol [15].

7.3 Selection of study population

7.3.1 Inclusion criteria

A patient must fulfill the following criteria in order to be included in the study:

1. Signed and dated informed consent provided by the patient, or the patient's legally authorized representative for patients under the legal age. Assent should be obtained from pediatric patients according to local regulations
2. Male patients of any age diagnosed with severe haemophilia A, as confirmed from the medical record
3. Previously treated with any plasma-derived or recombinant conventional or extended half-life FVIII
4. Diagnosed with high titer inhibitors (historical peak ≥5 BU/mL according to medical records)
5. Inhibitor titer ≥0.6 BU at screening

6. Failed previous ITI attempt(s) with any plasma-derived or recombinant conventional or extended half-life FVIII product including the use of immunosuppressant. The attempt should be documented in the medical records and have 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
7. All patients must assure to practice effective contraception during the study and for 3 months after their last dose of study treatment. Acceptable forms of birth control include barrier method (e.g. male condom, female condom, cervical cap, diaphragm, contraceptive sponge).

7.3.2 Exclusion criteria

The presence of any of the following will exclude a patient from inclusion in the study:

1. Other coagulation disorder(s) in addition to haemophilia A
2. History of hypersensitivity reactions associated with any rFVIIIFc administration
3. High risk of cardiovascular, cerebrovascular, or other thromboembolic events, as judged by the investigator
4. Planned major surgery to be deferred after study completion. Minor surgery such as tooth extraction or insertion/replacement of central venous access device is allowed.
5. Concurrent systemic treatment with immunosuppressive drugs within 12 weeks prior to screening. Exceptions to this include: ribavirin for treatment of HCV, and/or systemic steroids (a total of 2 courses of pulse treatments lasting no more than 7 days within 12 weeks prior to Day 1) and/or inhaled steroids
6. Abnormal renal function (serum creatinine >1.5 mg/dL or 2× upper limit of normal (ULN) for subject age based on local laboratory range) as assessed by local laboratory
7. Serum alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >5 × ULN as assessed by local lab
8. Serum total bilirubin >3 × ULN as assessed by local lab
9. CD4 lymphocytes ≤200 mm^3 if known as HIV antibody positive at Screening
10. Viral load of ≥400 copies/mL if known as HIV antibody positive at Screening
11. Patients with a documented history of alcohol or substance abuse within 12 months prior to randomization
12. Previous enrollment in this study (rescreening is allowed)

13. Participation in another concurrent clinical interventional study within 30 days of screening or intake of an investigational drug within five half-lives of that investigational drug has passed
14. Foreseeable inability to cooperate with given instructions or study procedures
15. Presence of any medical or psychological condition or laboratory result that in the opinion of the investigator can interfere with the patient's ability to comply with the protocol requirements or makes the patient not appropriate for inclusion to the study and treatment with rFVIIIFc
16. Concurrent treatment with emicizumab or previous use of emicizumab within five half-lives of emicizumab has passed unless laboratory analysis shows the level of emicizumab < lower level of detection

Exclusion criteria 9 and 10 refer to tests performed within 26 weeks prior to Screening. If results are not available, a new test should be drawn at the screening visit and analyzed locally prior to inclusion.

7.3.3 Withdrawal of patients from treatment or study

A patient should be withdrawn from the study treatment and discontinue the study for any one of the following reasons:

- ITI treatment is interrupted for >2 weeks
- Emergent or elective major surgery. Minor surgery such as tooth extraction or insertion/replacement of central venous access device is not a criterion for withdrawal.
- The patient received systemic treatment with chemotherapy and/or other immunosuppressant drugs. Use of corticosteroids for the treatment of asthma or management of acute allergic episodes is allowed with the exception of systemic corticosteroid treatment given to children daily or on alternate days at ≥2 mg/kg per day of prednisone or its equivalent or ≥20 mg/day if the duration is longer than 14 days.
- The patient is receiving concomitant immunomodulation.
- The patient is receiving emicizumab.
- The patient uses FVIII products other than rFVIIIFc (exception allowed for 1 emergency or accidental use).
- The patient or his legally authorized representative withdraws consent.
- If, in the clinical judgment of the investigator, it is not in the patient's best interest to continue with the study treatment.
- The patient enrolls into another interventional clinical study in which an investigational treatment or approved therapy for investigational use is administered.
- The patient is unwilling or unable to comply with the protocol.

The reason for the patient's withdrawal from the study must be recorded in the patient's case report form (CRF).

When a patient is withdrawn, the date of last rFVIIIFc dose and the date and reason for withdrawal (see above) should be clearly described in the relevant sections of the CRF. If a patient is removed from treatment because of an adverse event (AE), the reason for treatment withdrawal should always be stated as 'adverse event' irrespective of whether this was the investigator's or the patient's decision. The patients should be followed until the event has resolved, stabilized or returned to baseline.

The withdrawn patient should be examined, whenever possible, irrespective of the reason for withdrawal, as soon as possible. Relevant samples should be obtained and all relevant assessments should be completed, preferably according to the schedule for end of treatment visit. The CRF should be completed.

7.3.4 Replacement of withdrawn patients

Patients withdrawn prior to first dose will be replaced. Withdrawn patients who received at least one dose of rFVIIIFc will not be replaced.

7.4 Treatments

7.4.1 Identity of investigational medicinal products

Possible deficiencies related to the handling and quality of rFVIIIFc should be reported to the study monitor and also directly to complaints@sobi.com.

7.4.1.1 Europe and Canada

The investigational medicinal product rFVIIIFc is provided as a powder and solvent for solution for injection.

Each pack of rFVIIIFc contains 1 powder vial, 3 mL solvent in pre-filled syringe, 1 vial adapter, 1 infusion set, 2 alcohol swabs, 2 plasters and 1 gauze pad.

Powder:

The active substance is efmoroctocog alfa (recombinant coagulation factor VIII, Fc fusion protein). Each vial of rFVIIIFc contains nominally 250, 500, 1000, 2000 or 3000 IU efmoroctocog alfa.

The other ingredients are sucrose, sodium chloride, L-Histidine, calcium chloride dihydrate, polysorbate 20, sodium hydroxide and hydrochloric acid.

Solvent:

3 mL water for injections

The manufacturing of drug substance and drug product for the clinical study will not differ from the manufacturing of commercial available ELOCTA® and ELOCTATE® up to primary

packaging. Sobi will provide unlabeled rFVIIIFc drug product in its primary package to CRO who will package and label before distributing it to the study centers/designated local distributor.

Investigational medicinal product will be dispensed in accordance with national requirements. Home delivery of investigational medicinal product may be offered in compliance with national requirements.

rFVIIIFc should be stored and shipped refrigerated (2°C - 8°C) in the original pack. After dispensing, rFVIIIFc may be stored at room temperature (up to 30°C) for a single period not exceeding 6 months. After storage at room temperature, the product must not be put back in the refrigerator. rFVIIIFc should be stored at all times in the original pack in order to protect from light.

Once rFVIIIFc has been prepared it should be used immediately, or within 6 hours. The prepared solution should not be refrigerated and should be protected from direct sunlight. The prepared solution will be clear to slightly opalescent and colorless. Do not use the solution if it is cloudy or contains visible particles.

Labeling will comply with national regulatory requirements.

7.4.1.2 USA

In USA, commercial available ELOCTATE® in different vial strengths, with auxiliary labeling for clinical trial use, will be used as rFVIIIFc supply.

Auxiliary labeling will include information regarding sponsor name and contact details, clinical study number, kit number and patient number. ‘For clinical trial use only’ and ‘Keep out of reach of children’ will also be included.

ELOCTATE® is supplied in kits comprising a single use vial containing nominally 250, 500, 1000, 2000, or 3000 IU, a pre-filled syringe with 3 mL sterile water for injection, and a sterile vial adapter. Sites will be supplied with infusion sets, alcohol swabs, plasters and gauze pads separately.

ELOCTATE® should be stored and shipped refrigerated (2°C - 8°C/36°F-46°F) in the original pack. After dispensing, ELOCTATE® may be stored at room temperature (up to 30°C/86°F) for a single period not exceeding 6 months. After storage at room temperature, the product must not be put back in the refrigerator. ELOCTATE® should be stored at all times in the original pack in order to protect from light.

The reconstituted product may be stored at room temperature, not to exceed 30°C (86°F), for up to 3 hours. Protect from direct sunlight. After reconstitution, if the product is not used within 3 hours, it must be discarded. Do not use ELOCTATE® if the reconstituted solution is cloudy or has particulate matter.

Investigational medicinal product will be dispensed in accordance with national requirements. Home delivery of investigational medicinal product may be offered in compliance with national requirements.

7.4.2 Selection of doses

Refer to Section 7.2.2 for the rationale for the selected dosage regimen, dose levels and treatment duration.

During the ITI period the initial rFVIIIFc dose administered is 200 IU/kg/day, which may be given as once daily doses, or divided in two doses per day. If FVIII:C levels raise above 200 IU/dL already at a low-titer inhibitor (< 5 BU/mL), and before all three tolerance criteria have been confirmed, the dose should be decreased according to investigator judgment to maintain the peak FVIII:C levels between 100-200 IU/dL.

During the initial part of the tapering period the rFVIIIFc dose administered should be adjusted according to investigator judgment based on the FVIII:C results to maintain the peak FVIII:C levels between 100-200 IU/dL, with an aim to taper the FVIII:C levels to reach prophylactic levels as judged by the investigator after 16 weeks. Examples of different tapering approaches are provided in the pharmacy manual. FVIII:C levels should be ≥1 IU/dL at all time points during the tapering period. The duration of the tapering period may be adjusted after approval by the sponsor´s medical director however the dose should be decreased over at least 16 weeks.

During the follow-up period, the prophylaxis regimen should be adjusted based on clinical response, and with an aim to keep FVIII:C levels ≥ 1 IU/dL at all time points according to investigator judgment and local practice.

The patients should be instructed not to take a double dose to compensate a forgotten dose; instead, the next dose of rFVIIIFc should be taken on schedule the next day or according to the instructions of the investigator.

Bleeding episodes occurring during the ITI period should be treated according to investigator judgment and local practice. The use of bypassing agents such as aPCC and rFVIIa will be allowed but patients should be instructed to contact the investigator. Prescription of bypassing agents should be according to investigator´s judgment and local practice and if not in accordance with local label the medical monitor is to be notified and the rationale documented. The prophylactic prescription of bypassing agents requires notification by the investigator to the medical monitor and documentation of rationale.

Bleeding episodes in patients with low-titer inhibitors (<5 BU/mL) during the ITI period where the investigator judge that rFVIIIFc can provide sufficient hemostatic control, as well as in patients during the tapering and follow-up period should be treated with rFVIIIFc, with doses according to investigator judgment and local practice. In specific situations, e.g. if bleeding is unresponsive to treatment with rFVIIIFc, treatment with bypassing agents may be considered, as judged by the investigator. Such use is to be notified to the medical monitor and the rational documented in the medical records.

After the end of treatment visit, the patient should be treated according to investigator judgment and local practice. No further investigational medicinal product will be provided.

7.4.3 Selection and timing of doses for each patient

7.4.3.1 Administration of rFVIIIFc

After dissolving the powder for injection with the solvent supplied in the pre-filled syringe, rFVIIIFc will be delivered via a slow push IV injection over several minutes, at a rate of administration determined by the patient's comfort level.

As a precautionary measure, the initial administration of rFVIIIFc should be performed under medical observation, where proper medical care for allergic reactions could be provided. Patients/caregivers will be instructed to administer subsequent rFVIIIFc doses at home with the exception of the dose given in conjunction with study visits.

The patient/caregiver must enter dosing information on rFVIIIFc and/or FVIII bypassing agents into the diary as soon as possible after an injection, to ensure data integrity, and to facilitate appropriate medical review and dosing guidance. It is recommended that patients/caregivers enter dosing information immediately after an injection.

Complete instructions for the preparation and administration of rFVIIIFc are provided in the pharmacy manual and the patient information.

7.4.3.2 Dose calculations

The nominal strength is defined as the target potency of the vial (that is, 250 IU, 500 IU, 1000 IU, 2000 IU, or 3000 IU per vial). Nominal strength will be used for all calculations of rFVIIIFc dose and whole vials will be used to achieve the target dose, rounded to the nearest 250 IU. Per investigator judgment, it is also allowed to round up to the nearest 500 IU to decrease the number of vials used per injection.

7.4.4 Prior and concomitant therapy

A prior or concomitant therapy is any drug or substance administered from 30 days prior to the screening visit through the final safety follow-up visit. For patients who are receiving breast milk, any drug or substance being administered to the mother during the period when she is breastfeeding will also be considered a concomitant medication. Maternal concomitant medications will also be collected, unless the breast milk is derived from a source other than the mother. Maternal concomitant medications will no longer be collected after the discontinuation of breastfeeding.

The patients/caregivers should be instructed that the patient not start taking any new medications, including nonprescription drugs and herbal preparations, unless they have received permission from the investigator.

Allowed Concomitant Therapy

Concomitant use of bypassing agents such as aPCC and rFVIIa will be allowed as described in Section 7.4.2.

Therapy considered necessary for the patient's welfare, including routine immunizations, may be given at the discretion of the investigator. Concomitant medications must be recorded in the CRF. Prescribed doses of FVIII bypassing agents will be documented in the CRF by the investigator while the patient/caregiver must enter actual dosing information on FVIII bypassing agents into the diary. AEs related to administration of these therapies must be documented in the CRF.

Disallowed Concomitant Therapy

No other drug under investigation may be used concomitantly with the study treatment. Patients are not allowed to participate concurrently in another clinical study.

The following concomitant medications are not permitted through the end of treatment visit:

- Acetylsalicylic acid
- Current systemic treatment with chemotherapy and/or other immunosuppressant drugs. Use of corticosteroids for the treatment of asthma or management of acute allergic episodes is allowed with the exception of systemic corticosteroid treatment given to children daily or on alternate days at ≥2 mg/kg per day of prednisone or its equivalent or ≥20 mg/day if the duration is longer than 14 days.
- Concomitant immunomodulation will not be allowed during the study
- Concomitant emicizumab therapy will not be allowed during the study
- Any other FVIII product

Withdrawal due to use of disallowed concomitant therapy is described in Section 7.3.3.

Patients should be instructed to contact their investigators before taking any new medications, including nonprescription drugs and herbal preparations.

Concomitant Procedures

A concomitant procedure is any therapeutic intervention (e.g., physical therapy) or diagnostic assessment (e.g., blood gas measurement, bacterial cultures) performed from 30 days prior to the screening visit until the final safety follow-up visit/telephone call. The diagnose for the therapeutic intervention will be recorded and the procedure described in the medical records and recorded in the CRF. AEs related to administration of these procedures must be documented on the appropriate CRF but not the procedure e.g. insertion of central venous access devices.

7.4.5 Treatment compliance

Prescribed dose and dosing frequency of rFVIIIFc will be documented in the CRF. The date and time of the rFVIIIFc administrations on Day 1 (Baseline) and the doses given in conjunction with study visits, which will be administered in the clinic, will be recorded in the CRF. The date, time, amount of and reason for rFVIIIFc administrations not done in conjunction with study visits will be recorded by the patient/caregiver in the diary.

Product accountability records will be kept. The pharmacy and the investigator must maintain accurate records demonstrating date and amount of packs received, to whom and by whom

administered or dispensed (patient -by- patient accounting), and accounts of returned packs and any packs accidentally or deliberately destroyed. All unused packs will be counted. Unless otherwise notified, the patient/caregiver should return all vials (used and unused) at each visit for full medication exchange and accountability. At the end of the study, any remaining packs will be returned to the CRO for destruction, or destroyed locally. In either case, a certificate of destruction must be issued.

7.5 Study assessments

7.5.1 Study schedule

7.5.1.1 Schedule of events

Table 1 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			

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
HLA allotyping[d]		X			
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 2 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	

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
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	
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	

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
Diary review, including review of bleedings and rFVIIIFc dosing accountability[i]	X	X	X	
Non-serious adverse events	X	X	X	X
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.

7.5.1.2 Screening Visit

A signed informed consent form must be obtained from the patient/the patient´s legally authorized representative prior to any study-related activities. If applicable, assent will be obtained in accordance with local requirements. Any SAE that occur after informed consent has been signed must be reported (see Section 7.5.6.1.4).

Data will be collected on medical and surgical history (see Section 7.5.2), prior and concomitant medication (see Section 7.4.4) and demographics (see Section 7.5.3).

Physical examination (see Section 7.5.6.4), vital signs, height and weight (see Section 7.5.6.3) and local laboratory safety assessments (see Section 7.5.6.2) will be performed. A sample will be drawn for inhibitor assessment (see Section 7.5.5.1) and exploratory analysis of anti-FVIII antibodies (see Section 7.5.8.2).

7.5.1.3 Visits during the ITI period

7.5.1.3.1 Baseline Visit

Once all inclusion and exclusion criteria have been reviewed and recorded (see Section 7.3.1 and 7.3.2) and the patient has been found eligible, the patient will be assigned an enrollment number.

Physical examination (see Section 7.5.6.4), vital signs and weight (see Section 7.5.6.3) and local laboratory safety assessments (see Section 7.5.6.2) will be performed.

Samples will be drawn for inhibitor assessment (see Section 7.5.5.1) and, if results are not available from medical records and consent is obtained from the patient/the patient´s legally authorized representative, also for analysis of FVIII mutation and HLA allotyping (see Section 7.5.4). Samples will also be drawn for exploratory analysis of anti-FVIII antibodies (see Section 7.5.8.2) as well as for immune cell characterization (see Section 7.5.8.1).

Information regarding any bleedings since last visit as well as concomitant therapy/procedures will be collected (see Section 7.4.4).

Any SAE that occur after informed consent has been signed must be reported (see Section 7.5.6.1). Any AE that occurs after first dose of rFVIIIFc has been administered must be reported (see Section 7.5.6.1.2).

Once all pre-dose assessments have been completed, the first dose of rFVIIIFc will be administered by the investigator or delegate.

Before discharge, rFVIIIFc will be dispensed and the patient/caregiver will receive training in how to prepare and inject rFVIIIFc. The patient/caregiver will also receive training on the patient diary.

7.5.1.3.2 Week 2 visit

Vital signs and weight (see Section 7.5.6.3) will be collected.

Samples will be drawn for assessment of inhibitor (see Section 7.5.5.1) and pre-dose FVIII:C (see Section 7.5.5.2) as well as for the exploratory assessment of anti-FVIII antibodies (see Section 7.5.8.2) and exploratory immune cell characterization (see Section 7.5.8.1).

Once all samples have been taken, rFVIIIFc will be administered. Patients should therefore be instructed to refrain from their morning dose on the day of the visit.

The patient diary data will be reviewed and rFVIIIFc dosing and any bleedings discussed. Information regarding concomitant therapy/procedures will be collected (see Section 7.4.4).

All AE/SAEs must be reported (see Section 7.5.6.1).

Before discharge, unused rFVIIIFc will be returned by the patient/caregiver if not otherwise agreed and new rFVIIIFc will be dispensed.

7.5.1.3.3 Interim ITI visit

The Interim visits will be performed every 4th week (±1 week) during the ITI treatment period, starting at ITI week 4 until negative titer (<0.6 BU/mL) is achieved.

Vital signs and weight (see Section 7.5.6.3) will be collected at each visit. Physical examination (see Section 7.5.6.4) and hematology, blood chemistry and urinalysis assessments will be performed every 12th week, starting from the ITI initiation (see Section 7.5.6.2).

Samples will be drawn for assessment of inhibitor (see Section 7.5.5.1), pre-dose FVIII:C (see Section 7.5.5.2) and for the exploratory assessment of anti-FVIII antibodies (see Section 7.5.8.2).

Once all samples have been taken, rFVIIIFc will be administered. Patients should therefore be instructed to refrain from their morning dose on the day of the visit. At the discretion of the Investigator, an unscheduled FVIII:C sample 30 minutes post-dose may be drawn and analysed at the local lab to monitor FVIII:C peak levels.

The patient diary data will be reviewed and rFVIIIFc dosing and any bleedings discussed. Information regarding concomitant therapy/procedures will be collected (see Section 7.4.4).

All AE/SAEs must be reported (see Section 7.5.6.1).

Before discharge, unused rFVIIIFc will be returned by the patient/caregiver if not otherwise agreed and new rFVIIIFc will be dispensed.

At the discretion of the investigator, and in accordance with local practice and regulations, study visits can be performed in another location than the clinic. Laboratory samples should be analysed by the the same local laboratory and AE/SAEs collection over the phone is allowed. Study visits in another location requires pre-approval by the medical monitor.

7.5.1.3.4 ITI outcome assessment visits

After negative titer is achieved, ITI outcome visits will be performed every 4th week (±1 week) until IR>66% of the expected IR is achieved or until 60 weeks of treatment. After IR>66% of the expected IR is achieved, visits will be performed every 2nd week (±3 days) until ITI success or 60 weeks of treatment.

Vital signs and weight (see Section 7.5.6.3) will be collected at each visit. Physical examination (see Section 7.5.6.4), hematology, blood chemistry and urinalysis assessments will be performed every 12th week, starting from the ITI initiation (see Section 7.5.6.2).

Samples will be drawn for assessment of inhibitor (see Section 7.5.5.1), pre-dose FVIII:C (see Section 7.5.5.2) and for the exploratory assessment of anti-FVIII antibodies (see Section 7.5.8.2).

Samples will be drawn for assessment of IR at visits occurring after negative inhibitor has been confirmed at two consecutive visits until IR >66% of the expected IR has been confirmed at two consecutive visits. For assessment of IR, samples are drawn pre- and postdose (see Section 7.5.5.2) and patients are therefore instructed to refrain from their morning dose on the day of the visit, as this will be administered during the study visit.

Samples will be drawn for assessment of half-life after that IR >66% of the expected IR has been confirmed at two consecutive visits. Assessment of IR will be performed from the same samples. For assessment of half-life a 24-hour wash-out is required and samples are drawn pre- and postdose (see Section 7.5.5.2).

rFVIIIFc will be administered after the inhibitor sample and the pre-dose FVIII:C sample have been drawn.

The patient diary data will be reviewed and rFVIIIFc dosing and any bleedings discussed. Information regarding concomitant therapy/procedures will be collected (see Section 7.4.4).

All AE/SAEs must be reported (see Section 7.5.6.1).

Before discharge, unused rFVIIIFc will be returned by the patient/caregiver if not otherwise agreed and new rFVIIIFc will be dispensed.

At the discretion of the investigator, and in accordance with local practice and regulations, study visits can be performed in another location than the clinic. Laboratory samples should be analysed by the the same local laboratory and AE/SAEs collection over the phone is allowed. Study visits in another location requires pre-approval by the medical monitor.

7.5.1.4 Visits during tapering period

Vital signs and weight (see Section 7.5.6.3) will be collected at each visit. Physical examination (see Section 7.5.6.4), hematology, blood chemistry and urinalysis assessments will be performed every 12th week, starting from the ITI initiation (see Section 7.5.6.2).

Samples will be drawn for assessment of inhibitor (see Section 7.5.5.1), and for the exploratory assessment of anti-FVIII antibodies (see Section 7.5.8.2). For assessment of IR (see Section 7.5.5.2), samples are drawn pre- and postdose. rFVIIIFc will be administered after the inhibitor sample and the FVIII:C pre-dose sample have been drawn. Patients are therefore instructed to refrain from their morning dose on the day of the visit.

A sample for exploratory immune cell characterization will be drawn at the first visit in the tapering period and at the end of the tapering period (see Section 7.5.8.1).

The patient diary data will be reviewed and rFVIIIFc dosing and any bleedings discussed. Information regarding concomitant therapy/procedures will be collected (see Section 7.4.4).

All AE/SAEs must be reported (see Section 7.5.6.1).

Before discharge, unused rFVIIIFc will be returned by the patient/caregiver if not otherwise agreed and new rFVIIIFc will be dispensed.

At the discretion of the investigator, and in accordance with local practice and regulations, study visits can be performed in another location than the clinic. Laboratory samples should be analysed by the the same local laboratory and AE/SAEs collection over the phone is allowed. Study visits in another location requires pre-approval by the medical monitor.

7.5.1.5 Visits during follow-up period

7.5.1.5.1 Week 28 and 40 visits

Physical examination (see Section 7.5.6.4) will be performed and vital signs and weight (see Section 7.5.6.3) collected.

Samples will be drawn for assessment of inhibitor (see Section 7.5.5.1) and the exploratory assessment of anti-FVIII antibodies (see Section 7.5.8.2). For assessment of IR (see Section 7.5.5.2), samples are drawn pre- and postdose and rFVIIIFc administered after the inhibitor sample and the FVIII:C pre-dose sample have been drawn. Patients are therefore instructed to refrain from their morning dose on the day of the visit.

The patient diary data will be reviewed and rFVIIIFc dosing and any bleedings discussed. Information regarding concomitant therapy/procedures will be collected (see Section 7.4.4).

All AE/SAEs must be reported (see Section 7.5.6.1).

Before discharge, unused rFVIIIFc will be returned by the patient/caregiver if not otherwise agreed and new rFVIIIFc will be dispensed.

7.5.1.5.2 End of treatment visit

Physical examination (see Section 7.5.6.4) will be performed and vital signs, height and weight (see Section 7.5.6.3) collected. Hematology, blood chemistry and urinalysis assessments will be performed (see Section 7.5.6.2).

Samples will be drawn for assessment of inhibitor (see Section 7.5.5.1) and the exploratory assessment of anti-FVIII antibodies (see Section 7.5.8.2). A sample for exploratory immune cell characterization will be drawn for patients who did not achieve ITI success (see Section 7.5.8.1).

Pharmacokinetic assessments to determine IR and half-life (see Sections 7.5.5.2), if deemed measurable based on pre-dose FVIII:C, will be performed. Patients are required to have at least a 24-hour washout period prior to the half-life assessment, samples are drawn pre- and postdose and rFVIIIFc administered in the clinic after the inhibitor sample and the FVIII:C pre-dose

sample have been drawn. Assessment of IR will be performed from the samples drawn for half-life assessment.

For patients where the half-life is not deemed measurable based on pre-dose FVIII:C, samples are drawn pre- and postdose for the assessment of IR only. rFVIIIFc will be administered in the clinic after the inhibitor sample and the FVIII:C pre-dose sample have been drawn. Patients are therefore instructed to refrain from their morning dose on the day of the visit.

The patient diary data will be reviewed and rFVIIIFc dosing and any bleedings discussed. Concomitant therapy/procedures will be discussed (see Section 7.4.4).

All AE/SAEs must be reported (see Section7.5.6.1).

Any unused medication will be returned to the site.

7.5.1.6 Safety follow-up visit

AEs, SAEs, and concomitant medications and procedures will be collected (see Section 7.5.6.1 and 7.4.4). The visit can be conducted either as a follow-up telephone call or in-person visit at the discretion of the investigator.

7.5.2 Medical history

Medical, surgical, haemophilia, inhibitor, bleeding and ITI history will be collected at the screening visit.

7.5.2.1 Medical and Surgical history

Medical and surgical history includes any significant medical condition and/or any significant surgical histories, plus the following: history of allergy/anaphylactic shock, HIV infection status, hepatitis B infection status, hepatitis C infection status and any other congenital immunodeficiency. If a patient is known to be infected with HIV the following tests have to be performed at screening, unless results are available not older than 26 weeks: viral load, anti-HIV-1 and anti-HIV-2, cluster of differentiation 4 [CD4] count, and platelets. In the same way patients known to be infected with hepatitis B need to be tested for HBsAg, anti-HBc and anti-HBs; patients known to be infected need to be tested for anti-HCV (unless results are available no older than 26 weeks).

7.5.2.2 Haemophilia history

Haemophilia history includes the date of diagnosis, severity of disease, family history of haemophilia and inhibitors, genotype, blood group and number of exposure days to FVIII products prior to screening. Treatment regimen of any FVIII product and/or bypassing agent in the 12 months prior to baseline.

7.5.2.3 Inhibitor history

Inhibitor history includeslast dose, regimen and product used before inhibitor development, date and level of peak historical inhibitor titer, age at the time of inhibitor detection and exposure days at inhibitor development.

7.5.2.4 Bleeding history

Bleeding history in the 12 months prior to baseline includes date, location of bleeding, type of bleeding episode (e.g., spontaneous, traumatic) and treatment of the bleed.

7.5.2.5 ITI history

ITI history includes dose, regimen, type of FVIII (recombinant, plasma derived with von Willebrand factor or plasma derived without von Willebrand factor), other therapy (e.g. immunomodulation), start and stop date for previous ITI treatments, inhibitor titers, interruptions and reason for failure.

7.5.3 Demography

The patient's age at screening, gender, race, ethnicity, geographic location, body weight and height will be recorded in the CRF at the screening visit. The body weight recording will be repeated at each visit. Height will also be recorded at the end of treatment visit.

7.5.4 Analysis of FVIII mutation and HLA allotyping

For patients who's FVIII mutation and HLA allotype is not documented in medical records, samples for analysis of FVIII mutation and HLA allotyping will be collected at the baseline visit or any subsequent visit if blood volume is limiting at the baseline visit.

Analysis of FVIII mutation and HLA allotyping requires separate consent from the patients/ the patient's legally authorized representative. The assessment is optional and is not an inclusion or exclusion criterion; refusal of the patients/ the patient's legally authorized representative, or local laws precluding this test, would not exclude the patient from the study.

Analysis of FVIII mutation may provide information regarding the predisposition of genotypic subpopulations to experience different bleeding frequencies or different ITI outcomes. One of the decisive risk factors for the development of inhibitors is the type of mutation (e.g., full or missense) that codes for a protein that may be absent, truncated, or present but not functional. There is a correlation between the resultant protein and the likelihood of developing inhibitors to factor replacement [39].

Another factor that may impact inhibitor development or on achieving tolerance is the HLA allotype involved in antigen presentation to the T cells of the adaptive immune system.

The procedures for blood collection, processing, storing and transporting to the central laboratory as well as the laboratories responsible for the analysis are fully described in the laboratory manual.

7.5.5 Efficacy assessments

7.5.5.1 Assessment of inhibitor titers

7.5.5.1.1 Sampling procedure and bioanalytical method

Pre-dose blood samples for the determination of FVIII inhibitors will be collected at all visits during the study. Samples will be analyzed at the local laboratory using the Nijmegen-modified Bethesda assay and local procedures for blood collection and processing will be followed. The local laboratory that perform the determination of FVIII inhibitors should be accredited or participate in an external quality assurance scheme, e.g. United Kingdom National External Quality Assessment Service (UK NEQAS). The results from the local laboratory will constitute the primary data of the study to be used for statistical analysis.

Inhibitor samples will also be analyzed centrally using the validated Nijmegen-modified Bethesda assay. The procedure for blood collection, processing into plasma, storing, and transporting to the central laboratory as well as the laboratory responsible for the analysis are fully described in the laboratory manual. The results from the samples analyzed centrally will only be used for exploratory purposes and cannot overrule the primary data from the local laboratories. However, if the results from the local laboratory cannot be interpreted, the investigator may use the results from the central laboratory and in such case the investigator may base the assessment of ITI outcome on the results from the central laboratory.

Patients have fulfilled the first criterion for ITI success after a negative inhibitor titer (<0.6 BU/mL by the Nijmegen-modified Bethesda assay) has been determined locally at 2 consecutive determinations (Section7.1.2).

7.5.5.2 Assessment of incremental recovery and half-life

7.5.5.2.1 Sampling schedule

7.5.5.2.1.1 Pre-dose FVIII:C

At each visit where IR or t½ is not assessed, only a single pre-dose blood sample will be collected for monitoring of FVIII:C, starting from the Week 2. Patients should be instructed to refrain from their morning dose on the day of the visit as it will be administered during the visit.

7.5.5.2.1.2 Incremental recovery

Blood samples will be collected for analysis of FVIII:C for assessment of IR where t½ is not assessed, starting at the visit after confirmed negative titer.

Samples will be drawn within 30 minutes prior to and 30 (±5) minutes after the rFVIIIFc injection. The dose used will be the same as the prescribed dose at the time of the visit. Patients

should be instructed to refrain from their mo rning dose on the day of the visit as it will be given during the visit.

7.5.5.2.1.3 Half-life

Blood samples will be collected for analysis of FVIII:C for assessment of half-life starting at the visit after confirmed IR >66% of the expected IR. The assessment will be repeated at each consecutive visit until the elimination half-life is ≥ 7 hours and also at the end of treatment visit.

Samples will be drawn within 30 minutes prior and 30 (±5) minutes, 24 hours (±60 minutes), 30 hours (±60 minutes), and 48 hours (±60 minutes after the rFVIIIFc injection. The dose used will be the same as the prescribed dose at the time of the visit. Patients are required to have at least a 24-hour washout prior to the half-life predose sample collection and should not have any additional doses of rFVIIIFc during the PK sampling period. If emergency dosing is required during the assessment of half-life, please contact the medical monitor for instructions for how/when to repeat the assessment.

7.5.5.2.2 Sampling procedures and bioanalytical method

According to the local standard of care, an IV access device may be offered to facilitate sample collection. The IV access device is not to be flushed with heparin between injection of rFVIIIFc and the collection of the samples. If heparin must be used, standard technique for cleaning the infusaport of heparin must be employed.

rFVIIIFc will be delivered via a slow push IV injection over several minutes, at a rate of administration determined by the patient's comfort level. Volume and units of factor infused must be calculated and recorded using the nominal potency as described in the pharmacy manual.

Samples will be analyzed at the local laboratory using the local laboratory's standardized analytical procedure (one-stage aPTT or chromogenic substrate assay) and local procedures for blood collection and processing will be followed. The local laboratory that performs the determination of FVIII:C should be accredited or participate in an external quality assurance scheme, e.g. UK NEQAS. The results from the local laboratory will constitute the primary data of the study to be used for statistical analysis.

Samples will also be analyzed centrally using a validated one-stage clotting assay. The procedures for blood collection, processing into plasma, storing and transporting to the central laboratory as well as the laboratories responsible for the analysis are fully described in the laboratory manual. The results from the samples analyzed centrally will only be used for exploratory purposes and cannot overrule the primary data from the local laboratories. However, if the results from the local laboratory cannot be interpreted, the investigator may use the results from the central laboratory and in such case the investigator may base the assessment of ITI outcome on the results from the central laboratory.

7.5.5.2.3 Calculations

7.5.5.2.3.1 Incremental Recovery

IR will be calculated as the difference between the FVIII:C level at 30±5 minutes postdose ($C_{30\ min}$) and the FVIII:C predose level ($C_{predose}$) divided by the nominal dose, i.e.
IR = ($C_{30\ min} - C_{predose}$) / Dose [IU/kg].

FVIII:C levels below the lower limit of quantitation (LLOQ) will treated as zero.

Calculations of IR will be done by the investigator or designee.

Patients have fulfilled the second criterion for ITI success after an IR >66% of the expected IR has been determined at 2 consecutive determinations (Section 7.1.2). The expected IR for each patient will be documented by the investigator in the medical records.

7.5.5.2.3.2 Half-life

The elimination half-life will be calculated from the estimated terminal slope (λ_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. Calculations of elimination half-life will be performed by the CRO according to the following procedure:

(i) Estimate the terminal slope (λ) 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;
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 analyzed by non-compartmental analysis (NCA) using Phoenix WinNonlin v. 6.3.

Patients have fulfilled the third and last criterion for ITI success after a elimination half-life ≥7 hours has been determined (Section 7.1.2)

7.5.5.3 Assessment of bleeding episodes

7.5.5.3.1 Definition of a bleeding episodes

Only bleeds requiring treatment with rFVIIIFc or bypassing agents should be registered. A bleeding episode starts from the first sign of a bleed and ends no more than 72 hours after the last injection of rFVIIIFc or bypassing agents to treat the bleeding episode. Any symptoms of bleeding at the same location or injections less than or equal to 72 hours apart, are considered the same bleeding episode. Any injection of rFVIIIFc (or bypassing agents during the ITI period) to treat the bleeding episode, taken more than 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.

7.5.5.3.2 Type of bleeding episode

When a bleeding episode or hemorrhage is reported, it will be classified as 1 of 2 types: spontaneous or traumatic.

Spontaneous bleeding episodes

Bleeding episodes should be classified as spontaneous if a patients/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 patient/caregiver needs to be instructed by the investigator.

Traumatic bleeding episodes

Bleeding episodes should be classified as traumatic if the patient/caregiver records a bleeding episode even when there is a known or believed reason for the bleed. For example, if a patient were to exercise strenuously and then have a bleeding episode in the absence of any obvious injury, the bleeding episode would still be recorded as traumatic. Target joint bleeding episodes can be traumatic if a known action led to bleeding into the joint. The investigator should consider whether events resulting in a traumatic bleeding episode qualify as AEs i.e. is clinically significant, and should be reported as such. If hospitalization is required, an SAE should be reported.

7.5.5.3.3 Data to be captured

In the event of a bleeding episode, the following information should be collected in the diary or CRF:

- The type of bleeding episode (that is, spontaneous or traumatic) and if related to sports activity or physical activity
- The date the bleeding event occurred
- The product (rFVIIa, aPCCs, rFVIIIFc [include specific drug name], etc.) and dose administered to treat the bleeding episode including any repeat doses
- The location of the bleed

The patient diary will serve as the source document for bleeding episodes between visits. Bleeding episodes during study visits will be recorded in the CRF.

The clinical sites and Clinical Monitors will ensure that there is consistency between the patient's medical record, dispensing records, source documents, diary, and CRFs. During the study visits the investigator will verify whether or not a bleeding episode has occurred and was "spontaneous" or "traumatic." The patient/caregiver will also be reminded about timely diary completion.

Bleeding episodes will not be reported as AEs unless they fulfill the criteria for an SAE; however, the concomitant events associated with a bleeding episode should be reported as AEs as appropriate (e.g., a fracture in an elbow).

7.5.6 Safety assessments

7.5.6.1 Adverse events

7.5.6.1.1 Definitions

Adverse event

An Adverse event (AE) is any untoward medical occurrence in a 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 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 AEs. Bleeding episodes that meet a serious criterion should be reported as an SAE. All bleeding episodes that occur outside the study visit will be captured in the diary that the patient or the patient's caregivers will be maintaining throughout the study period.

Adverse events include the following:

- Abnormal test findings, as specified below.
- Clinically significant signs and symptoms.
- Changes in physical examination findings, i.e. worsening from baseline
- Progression/worsening of underlying disease.

In addition, signs and symptoms resulting from the following should also be handled according to the same principles as Adverse Events:

- Overdose
- Withdrawal of treatment
- Interactions
- Abuse
- Misuse

Overdose

An overdose is any dose of study treatment given to a subject or taken by a subject that exceeds the dose described in the protocol. Overdoses are not considered AEs; however if an overdose results in an AE, the AE must be recorded. Dosing information is to be recorded on the CRF.

Abnormal test findings

An abnormal test finding, e.g. abnormal laboratory analysis results, vital signs or ECG, should be recorded as an Adverse Event in any of the following situations:

- The test is associated with accompanying symptoms. Note, that the symptom, not the test result, should be recorded as an AE.
- The test result leads to a medical/surgical intervention (the medical condition for which the procedure was performed should be reported record), including withdrawal of rFVIIIFc or discontinuation from the study. Repeat/confirmatory testing is not considered a medical intervention.
- The investigator considers the test result to be clinically significant.

Preexisting conditions

A preexisting condition (i.e., a disorder present before the adverse event reporting period started and noted on the pretreatment medical history/physical examination form) should not be reported as an adverse event unless the condition worsens or episodes increase in frequency during the adverse event reporting period.

Procedures

Diagnostic and therapeutic non-invasive and invasive procedures, such as surgery, should not be reported as adverse events. However, the medical condition for which the procedure was performed should be reported if it meets the definition of an adverse event. For example, an acute appendicitis that begins during the adverse event reporting period should be reported as the adverse event and the resulting appendectomy entered in the comments section of the CRF.

Lack of efficacy

If there is a relapse of inhibitor after initial successful ITI this will be captured as an SAE, “relapse of inhibitor” and not as “lack of efficacy”.

Serious adverse event (SAE)

An adverse event that meets one or more of the following criteria/outcomes is classified as serious:

- 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).

Other medically important adverse events that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon appropriate medical

judgment, they may jeopardize the patient or may require medical or surgical intervention to prevent one of the outcomes listed above. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization or development of dependency or abuse.

In this study, the following events are considered medically important and must be reported as SAEs:

- 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 [WHO Handbook 1979] [40]:
  - Grade 2: bronchospasm; no parenteral therapy needed
  - Grade 3: bronchospasm; parenteral therapy required
  - Grade 4: anaphylaxis

  Allergic reactions, including anaphylaxis, have been reported with FVIII products. The patients/caregivers should be informed of early symptoms and signs of hypersensitivity reactions, including difficulty breathing, chest tightness, swelling of the face, rash, or hives. If such an event occurs while the subject is at home, the patients/caregivers should be instructed to seek immediate medical care for the subject.
- A patient develops a vascular thrombotic event, with the exception of IV injection site thrombophlebitis

  The patient and/or the patient´s legally authorized representatives will be informed of the early symptoms and signs of thrombotic phenomena, including pain and/or tenderness along a vein, unexpected swelling of an arm or leg without pain or tenderness, redness along a vein, low fever without any known reason (such as a cold or flu), sudden shortness of breath or difficulty breathing, or coughing, sudden chest pain, sudden severe headache or changes in vision, and numbness or tingling in arms or legs. If such an event occurs while the patient is at home, the patient and/or the patient's caregivers will be instructed to seek immediate medical care for the patient.

Serious also includes any other event that the investigator or company judges to be serious. Any suspected transmission of an infectious agent via rFVIIIFc shall also be considered serious.

Hospitalization

Hospitalization includes transfers within a hospital (e.g. from the psychiatric unit to the intensive care unit) and also includes admissions less than 24 hours. The following situations are not considered hospitalizations (although other SAE criteria may still apply):

- Outpatient procedures / ambulatory care
- Emergency department visits

Hospitalization in the absence of an adverse event occurring during the study should not be considered an SAE. This includes:

- Hospitalization due to a pre-existing condition not associated with a worsening of the pre-existing condition
- Protocol specified admission
- Pre-planned admission for a condition specified at baseline for the patient

If a patient is hospitalized due to local requirements for administration of study treatment, the hospitalization should not be considered an SAE unless another criterion/outcome for serious adverse event is fulfilled.

Suspected Unexpected Serious Adverse Reactions

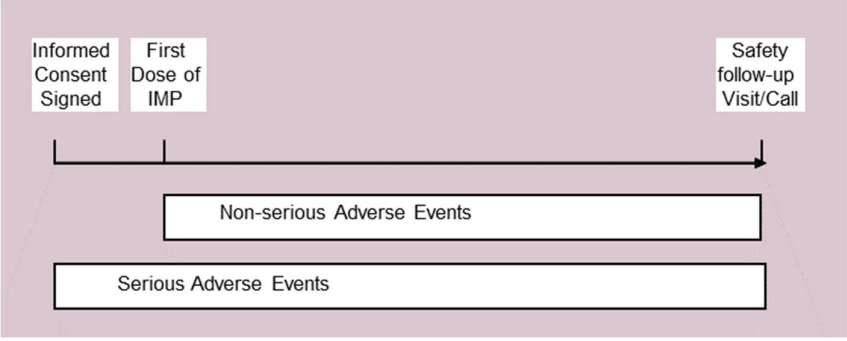
A Suspected Unexpected Serious Adverse Reaction (SUSAR) is an adverse reaction which is not consistent with the EU Summary of Product Characteristics (SmPC). The Sponsor will ensure that all relevant information about SUSARs involving the investigational medicinal product are reported to the relevant regulatory authorities and ethics committees in compliance with current national legislation. All SAEs are processed in the Global Safety Database held by the Sponsor's partner Bioverativ. Bioverativ is responsible for expedited reporting of SUSARs to Regulatory Authorities. Sponsor's CRO is responsible for the distribution of SUSARs to Central Ethic committees and investigators.

7.5.6.1.2 Adverse event reporting period

Any SAE experienced by the patient between the time of signature of the ICF and the safety follow-up visit is to be recorded in the CRF. In addition, any non-serious AE experienced by the patient between the time of first dose of investigational medicinal product and the safety follow-up visit is to be recorded in the CRF (Figure 3).

Furthermore, any SAE should be reported to the CRO irrespective of the time of occurrence if a causal relationship between the event and the rFVIIIFc is suspected.

Figure 3 Adverse event reporting period



7.5.6.1.3 Eliciting and recording adverse event information

The investigator is to record all directly observed adverse events, and all adverse events spontaneously reported by the patient, in the CRF using concise medical terminology. In addition, each patient will be questioned about adverse events at each study visit following initiation of treatment. The question asked will be "Since you began taking rFVIIIFc" have you had any health problems?"

When possible and appropriate, a diagnosis rather than individual signs and symptoms shall be recorded. The investigator is responsible for obtaining sufficient information to determine seriousness, causality and outcome of each adverse event.

Severity assessment

The investigator will use the adjectives MILD, MODERATE, or SEVERE to describe the maximum intensity of the adverse event. For the purpose of consistency, these intensity grades are defined as follows:

MILD	Does not interfere with patient's usual function
MODERATE	Interferes to some extent with patient's usual function
SEVERE	Interferes significantly with patient's usual function

Note the distinction between the gravity (seriousness) and the intensity (severity) of an adverse event. **Severe** is a measure of intensity; thus, a **severe** reaction is not necessarily a **serious** reaction. For example, a headache may be severe in intensity, but would not be classified as serious unless it met one of the criteria for serious events listed above.

Causality assessment

For each adverse event, the investigator must make a causality assessment to determine if there is a reasonable possibility that rFVIIIFc caused the adverse event. The adverse event is assessed as **related** or **not related** to rFVIIIFc.

7.5.6.1.4 Serious adverse event reporting

Both serious and non-serious adverse events are to be reported on the adverse event page of the CRF as specified in the CRF instructions.

If an SAE occurs, Drug Safety at the CRO is to be notified by entering required information about the SAE into the appropriate module of the CRF within 24 hours of awareness of the event by the investigator.

The form for collection of SAE information is not the same as the general adverse event CRF page. Where the same data are collected, the forms must be completed in a consistent manner. For example, the same adverse event term should be used on both forms.

All new information obtained, relevant to an SAE report, should be forwarded to CRO within the same timeframe as the initial information.

The investigator shall provide CRO/Sobi with sufficient information to enable a complete medical assessment of the reported event. Best efforts shall be made by the investigator to provide Sobi with additional information related to any SAE as requested.

7.5.6.1.5 Exposure during pregnancy

Congenital abnormalities in offspring of male subjects shall be reported as an SAE if conception occurs during the study period.

Pregnancy in male patient's partner shall be reported to Sobi (fax number + 46 8 697 32 30) or by e-mail to drugsafety@sobi.com promptly of awareness by any study personnel, whether the exposure is associated with an adverse event or not. Pregnancy itself will not be considered an AE.

In all reported situations of exposure during pregnancy, Sobi will provide the investigator with a Pregnancy Report Form which shall be completed and returned by the investigator. Sobi will make every effort to follow-up on the outcome of the pregnancy and offspring.

7.5.6.1.6 Follow-up of unresolved adverse events

All adverse events should be followed until they are resolved or the investigator assesses them as chronic or stable, or the patient's participation in the study ends, i.e., until last scheduled visit'. How to report changes in an ongoing adverse event during a patient's participation in the study is described in the CRF instructions.

In addition, all serious and non-serious adverse events assessed by the investigator as related to rFVIIIFc should continue to be followed until they resolve or until the investigator assesses them as "chronic" or "stable", even after the patient's participation in the study is over i.e. not to be recorded in the CRF.

7.5.6.2 Laboratory safety assessments

Blood samples for determination of hematology and biochemistry variables and urine samples will be collected at screening, baseline visit (before the first rFVIIIFc administration) and then every 12th week from the start of the ITI treatment period through the end of the tapering period. Blood and urine samples will also be collected at the end of treatment visit. The date of blood and urine 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 analyzed at a local laboratory. Clinically significant abnormal laboratory values should be reported as adverse events (see Section 7.5.6.1.1 for details). The corresponding result should be entered into the CRF together with information on laboratory variable assessed, date of sample, and normal range from the local laboratory.

7.5.6.3 Vital signs

Vital signs (blood pressure, pulse rate, respiratory rate and body temperature or any untoward reactions) will be assessed at each visit. Postdose assessments following rFVIIIFc injections should be taken approximately 20 minutes after the end of the injection.

Systolic and diastolic blood pressure, pulse rate and respiratory rate for 30 seconds will be measured according to each clinic´s standard procedures.

Body temperature will be measured using a tympanic thermometer according to each clinic´s standard procedures.

Clinically significant abnormal vital signs values should be reported as adverse events (see Section 7.5.6.1.1 for details).

7.5.6.4 Physical examination

A general physical examination will be assessed and recorded as "normal" or "abnormal" at screening, baseline visit (before the first rFVIIIFc administration) and then every 12th week from the start of the ITI treatment period through the end of the tapering period. It will also be assessed at each visit during the follow-up period. Abnormalities should be described. Any persisting abnormalities should be stated each time the examination is performed. Diagnosis of

new abnormalities should be recorded as adverse events. If any abnormalities are reported at baseline please ensure they are recorded as medical history.

7.5.6.5 Sample volumes

The volume of blood taken from the patients should comply with European Commission guidance [41], namely the study-related blood loss should not exceed 3% of the total blood volume during a period of 4 weeks and should not exceed 1% at any single time. Examples of recommended blood draw volume limits per the European Commission guidance are provided in Table 3. Local and/or regional guidelines regarding blood draw volumes may also apply.

Site specific tables with information of blood volumes per assessment and type of visit will be provided.

If it is not possible to collect the whole blood volume required for the assessments at a given visit, without exceeding the maximum allowed blood volume, smaller volumes will be collected. The blood will then be used for as many of the assays as possible with the following priority order:

- Local assessment of FVIII:C
- Local assessment of inhibitor titer
- Haematology and blood chemistry
- ADA assessment
- Central assessment of FVIII:C
- Central assessment of inhibitor titer
- Immune cell characterization

Table 3 Examples of recommended blood draw volume limits

Subject Weight (kg)	Blood Draw Limits (mL)[a]	
	Single Occasion[b]	4 weeks [b]
3.5	2.8	8.4
4.0	3.2	9.6
4.5	3.6	10.8
5.0	4.0	12.0
5.5	4.4	13.2
6.0	4.8	14.4
6.5	5.2	15.6
7.0	5.6	16.8
7.5	6.0	18.0

Subject Weight (kg)	Blood Draw Limits (mL)[a]	
	Single Occasion[b]	4 weeks [b]
8.0	6.4	19.2
8.5	6.8	20.4
9.0	7.2	21.6
9.5	7.6	22.8
10.0	8.0	24.0
10.5	8.4	25.2
11.0	8.8	26.4
11.5	9.2	27.6
12.0	9.6	28.8
12.5	10	30.0
13.0	10.4	31.2
13.5	10.8	32.4
14.0	11.2	33.6
14.5	11.6	34.8
15.0	12.0	36.0

[a] Based on an estimated blood volume of 80 mL/kg

[b] Based on European Commission guidance [41] recommending that blood draw volumes not exceed 1% of total blood volume on a single occasion or 3% over a 4-week period.

7.5.7 Pharmacoeconomic assessments

Prescribed dose and dosing frequency of rFVIIIFc and bypassing agents will be recorded in the eCRF. Consumption will be assessed based on amount of administered drug as recorded in the CRF and in the diary.

The date and time of administrations of rFVIIIFc and bypassing agents during the study visits will be recorded in the CRF by the investigator or designee. The date, time, dose and reason for administrations done not in relation with study visits will be recorded by the patient/caregiver in the diary.

Days patient missed from school or work will be recorded in the diary. Hospitalizations will be captured as SAEs.

7.5.8 Exploratory laboratory assessments

Inhibitor titers measured by the Nijmegen modified Bethesda assay in patient samples may reflect only part of an overall antibody response to factor VIII treatment. Antibodies have been detected in samples from hemophilia A patients applying immuno assays long before occurrence of inhibitors and inhibitors have been suggested to reflect the further maturation of the anti-FVIII immune response over time into antibodies of higher affinity and/or titers of in particular IgG1 and IgG4 subclasses [42,43]. FVIII binding antibodies have also been found in healthy subjects but with a difference in IgG subclass distribution compared to inhibitor patients that may suggest a difference in the regulatory pathways responsible for inhibitor development [42]. Moreover, non-neutralizing antibodies have been suggested to contribute significantly to FVIII half-life reduction in hemophilia A patients [44]. In order to obtain further understanding of mechanisms underlying rescue ITI success but also potential failure of rescue ITI with rFVIIIFc, the overall anti-FVIII antibody population present in the samples from patients will be further characterized in regards isotypes and overall titers in addition and parallel to the measurement of inhibitor titers and PK parameters. Furthermore an assessment will be made at a few occasions, covering prior to start of ITI treatment, the ITI treatment and tapering periods and the end of the study visit, of the immune cellular and cytokine profiles including regulatory T-cells.

7.5.8.1 Immune cell characterization

Whole blood samples will be collected for immune cell characterization at the baseline visit (predose) and ITI week 2. Upon successful ITI, a sample will be collected at the first visit in the tapering period and at the end of the tapering period. Upon partial success or failure of ITI a sample will be collected at end of treatment visit. Samples will be analyzed centrally.

The procedures for blood collection, preparation of cells, storing and transporting to the central laboratory as well as the laboratory responsible for the analysis are fully described in the laboratory manual.

Results of the exploratory immune cell characterization will be reported separately from this study.

7.5.8.2 Anti-rFVIII Antibody (ADA) Assessment

Blood samples will be collected for analysis of anti-FVIII antibodies (ADA) at the baseline visit and at all consecutive visits. Samples will be analyzed centrally using a validated MSD-ECL based bridging format immunoassay.

The procedures for blood collection, processing into plasma, storing, and transporting to the central laboratory as well as the laboratory responsible for the analysis are fully described in the laboratory manual.

A tiered approach will be applied including screening of samples, confirmation of a screened positive result and titer determination of confirmed positive samples. Samples with ADA may be further characterized with regards to antibody isotypes for exploratory purposes.

Results of the exploratory ADA assessments will be reported separately from this study.

8 Quality control and quality assurance

This study will be conducted in compliance with this protocol, study specific procedures, CRO SOPs, the ICH Guideline for Good Clinical Practice, and applicable regulatory requirements.

Monitoring visits to the study site will be performed periodically during the study, to help ensure compliance with the protocol, study-specific procedures and applicable regulatory requirements. Source documents will be reviewed for verification of agreement with data in CRFs. All patient informed consent forms will be reviewed. The investigator or institution guarantees access to source documents by Sobi, its representatives, and appropriate regulatory agencies.

The study site may be subject to a quality assurance audit by Sobi or its representatives, as well as inspection by appropriate regulatory agencies.

It is important that the investigator(s) and the(ir) relevant personnel are available during the monitoring visits and possible audits and that sufficient time is devoted to the process.

9 Statistical plan

9.1 Determination of 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.

9.2 Definition of study populations

The following analysis sets will be derived

- ITI full analysis set (ITIFAS): This set will include all patients receiving at least one dose of rFVIIIFc. All analyses describing efficacy and safety during ITI treatment will be based on this analysis set.
- Tapering period full analysis set (TPFAS): This set will include all patients entering the tapering period of the study. All efficacy and safety during the tapering period will be based on this analysis set. Analyses covering both the tapering period and the follow-up period (48-week Follow-up Period) will be based on TPFAS.

- Follow-up full analysis set (FUFAS): This set will include all patients entering the follow-up period in the study. Specific analyses concerning the follow-up period only will be based on this analysis set.

9.3 Overall statistical and analytical plan

9.3.1 General statistical issues

A study specific statistical analysis plan (SAP) containing a detailed description of all analyses to be conducted will be developed and finalized prior to database lock.

No formal statistical hypothesis testing will be performed. All endpoints will be summarized with descriptive statistics.

9.3.2 Demographics and baseline characteristics

Demographics and baseline characteristics will be summarized using descriptive statistics.

9.3.3 Analysis related to primary objective

The number and proportion of patients achieving ITI success, partial success and treatment failure will be calculated.

The ITIFAS analysis set will be used for this analysis.

Descriptive statistics of the levels of rFVIIIFc inhibitors will be calculated longitudinally for all visits during the ITI treatment period.

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.

The ITIFAS analysis set will be used for this analysis.

9.3.4 Analysis related to secondary objective

9.3.4.1 Time to ITI success

Time to ITI success will be analyzed descriptively using Kaplan-Meier estimates including median, 25th and 75th quartile. A Kaplan-Meier plot will be generated. Patients not achieving ITI success during the up to 60 weeks ITI period will be censored at the last observed time for this analysis. The ITIFAS analysis set will be used for this analysis.

Time to ITI success will also be summarized descriptively for the patients achieving ITI success.

Time to confirmed negative titer will be analyzed in the similar way.

Time to confirmed Incremental recovery >66% of the expected IR will be analyzed similarly as well on the subset of patients who reached confirmed negative titer.

For the subset of patients who were classified as partial success at the end of the ITI period, the time to fulfillment of the criteria for partial success will also be analyzed descriptively.

9.3.4.2 Occurrence of relapse

Occurrence of relapse will be summarized descriptively by calculating the proportion of patients with ITI success who reaches the criteria for relapse. The TPFAS set will be used for this analysis.

Time to relapse will be defined as the duration between the time of ITI success and time of relapse. Time to relapse will be summarized descriptively among those who relapsed.

9.3.4.3 Number of bleedings during ITI treatment.

Number of bleedings during ITI treatment will be summarized per month with descriptive statistics. The ITTFAS analysis set will be used for this.

9.3.4.4 Bleeding rate during 48-week follow-up period

The bleeding rate during the 48-week follow up period will be summarized with descriptive statistics. The rate for each patients will be annualized to account for potential differences in follow-up period. The TPFAS analysis set will be used for this analysis.

9.3.4.5 Consumption

Consumption during the ITI period will be calculated and summarized descriptively using the ITIFAS analysis set. Consumption will also be calculated for the Tapering and Follow-up periods separately using their respective analysis set.

9.3.4.6 Number of days missed school or work during ITI treatment

Number of days missed school or work during ITI treatment will be summarized descriptively. The ITIFAS analysis set will be used for this analysis.

9.3.4.7 Number of days missed school or work during a 48-week period

following successful ITI treatment

Number of days missed school or work during the 48-week period following ITI treatment will be summarized descriptively. TPFAS analysis set will be used for this analysis.

9.3.4.8 Number of hospitalizations during ITI treatment

Number of hospitalizations during ITI treatment will be summarized descriptively. The ITIFAS analysis set will be used for this analysis.

9.3.4.9 Number of hospitalizations during a 48-week period following successful ITI treatment

Number of hospitalizations during the 48-week period following ITI treatment will be summarized descriptively. TPFAS analysis set will be used for this analysis.

9.3.4.10 Adherence

Adherence with the treatment regimen will be calculated in 2 ways, as dose adherence and as dosing frequency adherence. Percentage of administered doses as registered in the diary versus prescribed doses and percentage of number of days with infusions as registered in the diary comparing to prescribed number of days will be summarized using descriptive statistics for each of the three periods separately. The respective analysis set will be used for each of the periods.

9.3.5 Analysis of safety and tolerability data

9.3.5.1 Adverse events

Reported adverse events during the study will be coded using MedDRA. The number of patients with any adverse events occurring after first dose of rFVIIIFc will be summarized in frequency tables, system organ class, preferred term, and maximum severity. Listings of adverse-event subgroups such as serious adverse events and adverse events leading to discontinuation will be also presented.

Separate tabulations of adverse events, serious adverse events and non-serious adverse events will be made for ITI period, including tapering period and follow-up period as well as across all periods.

9.3.5.2 Vital signs

Vital signs will be summarized descriptively by visit.

9.3.5.3 Exposure and Duration of Treatment

Duration of exposure and the total number of exposure days to rFVIIIFc will be summarized. An exposure day is a 24-hour period in which 1 or more rFVIIIFc injections are given.

9.3.6 Interim analysis

No formal interim analysis is planned.

9.3.7 Multiple comparison/multiplicity

As no formal hypothesis testing will be performed adjustment for multiple comparisons will not be applicable in this study.

9.3.8 Exploratory subgroup analyses

No particular subgroup analysis of interest has been identified but exploratory subgroup analyses may be performed if considered relevant and sufficient number of patients in each group is available. This will be described in further details in the SAP.

9.3.9 Handling of missing data

No imputation of missing data are planned.

10 Data collection, handling and record keeping

10.1 Data standards

Collection of data should be performed in the Clinical Data Acquisition Standards Harmonization (CDASH) format, according to the Clinical Data Interchange Standards Consortium (CDISC). The minimum requirement of the CDISC standard is to collect all core variables specified as ‘Required’ in the Study Data Tabulation Model (SDTM) format.

10.2 Case report form

A CRF is required and should be completed for each included patient. In this study an electronic CRF will be used. The completed original CRFs are the sole property of Sobi and should not be made available in any form to third parties, except for authorized representatives of appropriate Regulatory Authorities, without written permission from Sobi.

It is the responsibility of the investigator to ensure completion and to review and approve all CRFs. CRFs must be signed electronically by the investigator. These signatures serve to attest that the information contained on these CRFs is correct. At all times, the investigator has final responsibility for the accuracy and authenticity of all clinical and laboratory data entered on the CRFs.

10.3 Diary

Patients/caregivers will receive a diary at the baseline visit. The patient/caregiver must enter bleeding episodes and dosing information on rFVIIIFc and/or bypassing agents into the diary as soon as possible after an injection, to ensure data integrity, and to facilitate appropriate medical review and dosing guidance. It is recommended that patients/caregivers enter dosing information immediately after an injection. The diary data will be reviewed by the investigator together with the patient/caregiver at each visit.

10.4 Source data

Patient's source documents are the investigator's patient records maintained at the study site. In most cases, the source documents will be the hospital's or the investigator's chart. In those cases, the information collected on the CRFs must match those charts.

In some cases, a portion of the source documents for a given patient may be the CRF or the diary.

- In this study, the following are recorded as source data directly in the CRFs: rFVIIIFc and bypassing agent administration during study visits, race (if local law prevents this from being recorded in the medical records).
- In this study, the following are recorded as source data directly in the patient diary: rFVIIIFc and bypassing agent administration outside study visits, bleeding information

A source data location document will be completed by every site.

10.5 Database closure

Prior to database closure, all tasks or criteria defined in the data management plan must be completed and documented. The database lock will be approved by relevant study personnel and all edit accesses will be removed. The study database can only be unlocked in the event of critical errors, affecting the main conclusions of the study, are discovered.

10.6 Record retention

To enable evaluations and/or audits from Health Authorities or Sobi, the investigator agrees to keep records in accordance with the essential documents defined in the ICH GCP Guidelines [1], including the identity of all participating patients (sufficient information to link records, e.g., CRFs and hospital records), all original signed informed consent forms, an archival copy on compact disc of the electronic CRFs (provided by the CRO hosting the study database) and detailed records of rFVIIIFc accountability. The records should be retained by the investigator according to local regulations or as specified in the Clinical Trial Agreement.

If the investigator relocates, retires, or for any reason withdraws from the study, the study records may be transferred to an acceptable designee, such as another investigator, another institution, or to Sobi. The investigator must obtain Sobi's written permission before disposing of any records.

11 End of study

The end of this study is defined as the date of the last patient's last visit.

12 Sponsor's discontinuation criteria

Sobi reserves the right to discontinue the study prior to inclusion of the intended number of patients, but intends only to exercise this right for valid scientific or administrative reasons.

After such a decision, the investigator must contact all participating patients within 30 days. The investigator shall return to the CRO all unused investigational medicinal product and other study materials, and complete all the CRFs to the greatest extent possible.

13 Dissemination and publication of results

Sobi will register the study and post study results regardless of outcome on a publicly accessible website in accordance with applicable laws and regulations, e.g., www.clinicaltrials.gov and EudraCT. The results of this study will be published within 6 months of the end of study.

Sobi follows the principals of the International committee of medical journal editors recommendations for the conduct, reporting, editing, and publication of scholarly work in medical journals [45]. The data from this study may be considered for reporting at a scientific meeting or for publication in a scientific journal. The sponsor will be responsible for these activities and will work with the investigators to determine how the publication is written, the number and order of authors, the journal or scientific meeting to which it will be submitted, and other related issues. The results of the study, or any part thereof, shall not be published without the prior written consent and approval of Sobi, such consent and approval not to be unreasonably withheld.

14 References

1 ICH Harmonised Guideline: Integrated addendum to ICH E6 (R1), Guideline for Good ClinicalPractice E6(R2) Current *Step 4* version dated 9 November 2016. Available from: http://www.ich.org/products/guidelines/efficacy/article/efficacy-guidelines.html

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