Bioverativ Therapeutics Inc.
225 Second Avenue
Waltham, MA 02451

TRACKING NUMBER: **997HA402**

PHASE OF DEVELOPMENT: **4**

PROTOCOL TITLE: A Non-Controlled, Open-Label, Multicenter, Study of Efficacy of rFVIIIFc for Immune Tolerance Induction (ITI) in Severe Hemophilia A Subjects With Inhibitors Undergoing the First ITI Treatment

EUDRA CT NO: 2017-000373-36

DATE: **11 Jul 2019**
Version 3.0

Supersedes Version 2.0 dated 09 February 2018 and Version 2.1 dated 02 March 2018.

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SPONSOR SIGNATURE PAGE

Protocol 997HA402, V3.0 was approved by:

[redacted]

[redacted]

Date:

Rare Blood Disorders

Sanofi Genzyme

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PROTOCOL AMENDMENT SUMMARY OF CHANGES

DOCUMENT HISTORY

Document	Country/countries impacted by amendment	Date
Protocol Version 3	All, including Canada	11 July 2019
Protocol Version 2.1 (from Version 1.1)	Canada	02 March 2018
Protocol Version 1.1 (from Version 1)	Canada	06 July 2017
Protocol Version 2	All	09 February 2018
Protocol Version 1	All	19 January 2017

Present amendment to the protocol (11-July-2019)

This is a global amendment to the protocol V2.0 and V2.1, and includes specific requirements for Canada in Appendix B.

OVERALL RATIONALE FOR THE AMENDMENT

The primary reason for this amendment to Protocol 997HA402 is to reduce the number of subjects to be enrolled, to clarify the timing for subjects moving from interim ITI visits to ITI outcome assessment visits, and to clarify sample collection schedules for ADA. Additional updates have been made for Canada and these country-specific changes are outlined in Appendix B.

PROTOCOL AMENDMENT SUMMARY OF CHANGES

Section # and Name	Description of Change	Brief Rationale
Synopsis, Section 7.1, and Section 16.1.	Following texts or similar texts have been added in the sections: This study will enroll up to 17 subjects, Or Approximately, 17 subjects will be treated	The primary reason for this amendment to Protocol 997HA402 is to reduce the number of subjects to be enrolled, to clarify the timing for subjects moving from interim ITI visits to ITI outcome assessment visits, and to clarify sample collection schedules for ADA, and to incorporate requests by Health Canada.
Section 4.2, Section 7.2.2, Section 7.2.2.2, and Section 13.1.2.1	Clarification for the timing for subjects moving from interim ITI visits to ITI outcome assessment visits was added to the sections and Table 1, Table 1 footnote 13, Table 2 footnote 11, and Figure 2 were updated.	
Section 4.2 and Section 13.5.2	ADA sample collection has been clarified in Table 1, footnote 10.	
Section 4.2, Section 8.1, Section 13.5.4, Section 14.2, Section 15.4.1, Section 15.5.1, and Appendix B	Specific changes for Canada from Protocol 1.1 and 2.1	

Two new appendix sections have also been created to display history of protocol amendments (Appendix A) and country specific requirements (Appendix B).

1. SPONSOR INFORMATION

This study is sponsored by Bioverativ Therapeutics Inc. (Sponsor). Refer to the Study Reference Manual that contains all study contacts for complete contact information.

Bioverativ Therapeutics Inc.
225 Second Avenue
Waltham, MA 02451
USA

Bioverativ Japan Ltd.
Nihonbashi 1-chome Mitsui Building 14F
4-1 Nihonbashi 1-chome
Chuo-ku, Tokyo
103-0027 Japan

For urgent medical issues in which the study's Medical Director should be contacted, please refer to the Study Reference Manual Official Study Contact List for complete contact information.

Sponsor may transfer any or all of its study-related responsibilities to contract research organization (CRO) and other third parties; however, Sponsor retains overall accountability for these activities.

2. LIST OF ABBREVIATIONS

ADA	anti-drug antibody
AE	adverse event
aPCC	activated prothrombin complex concentrate
aPTT	activated partial thromboplastin time
BU	Bethesda Unit
CD4	cluster of differentiation 4
CHO	Chinese hamster ovary
CRO	contract research organization
DHA	Directions for Handling and Administration
ED	exposure day
EDC	electronic data capture
EHL	extended half-life
EOT	end of treatment
EPD	electronic patient diary
FEIBA	factor eight inhibiting bypassing activity
FVIII	coagulation factor VIII
GCP	Good Clinical Practice
HBV	hepatitis B virus
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HLA	human leukocyte antigen
ICF	informed consent form
ICH	International Council for Harmonisation
IITR	International ITI Registry
IQR	interquartile range
IR	incremental recovery
ITI	immune tolerance induction
ITIFAS	ITI full analysis set
IU	international units
IV	Intravenous
IXRS	Interactive Web Response System
NAITR	North American ITI Registry
NGNA	N-glycolylneuraminic acid
pdFVIII	plasma-derived FVIII
PK	pharmacokinetics
rFVIIa	recombinant activated factor VII
rFVIII	recombinant coagulation factor VIII
rFVIIIFc	recombinant coagulation factor VIII Fc fusion protein
SAE	serious adverse event
SAP	Statistical Analysis Plan

SUSAR	suspected unexpected serious adverse reaction
$t_{½}$	half-life
TPFAS	Tapering Period full analysis set
ULN	upper limit of normal
USA	United States of America
VWF	von Willebrand factor

3. SYNOPSIS

Tracking Number:	997HA402
Protocol Title:	**A Non-Controlled, Open-Label, Multicenter, Study of Efficacy of rFVIIIFc for Immune Tolerance Induction (ITI) in Severe Hemophilia A Subjects with Inhibitors Undergoing the First ITI Treatment**
Version Number:	2.0
Name of Study Treatment:	Antihemophilic factor VIII (recombinant) Fc fusion protein; rFVIIIFc; Eloctate®; Elocta®
Study Indication:	Hemophilia A, ITI
Phase of Development:	4
Rationale for the Study:	Hemophilia A (coagulation factor VIII [FVIII] deficiency) is a rare X-linked bleeding disorder and the most common type of hemophilia. The most serious treatment complication for patients with hemophilia A is the development of inhibitory immunoglobulin antibodies to FVIII. Inhibitors result in rapid clearance of infused FVIII and marked reduction, or absence, of efficacy of FVIII treatment. FVIII-bypassing agents such as activated prothrombin complex concentrate (aPCC [FEIBA]) or recombinant activated factor VII (rFVIIa [NovoSeven]) are used to treat acute bleeding in patients with high-titer inhibitors, but inhibitor eradication remains the goal of long-term management. Immune tolerance induction (ITI) therapy using frequent administration of high doses of FVIII is the only proven strategy shown to achieve antigen-specific tolerance (Kempton et al., 2014; Valentino et al., 2015). ITI usually attempts to eliminate high-responding FVIII inhibitors (≥5 Bethesda Unit [BU] titer). ITI regimens employ different doses and dosing frequencies of FVIII, and they may or may not involve adjunctive immunomodulatory therapy (Franchini et al., 2011; Valentino et al., 2015). Currently, a range of FVIII products and dosing regimens are used for ITI because there is no clear consensus on an optimal regimen (Franchini et al., 2011).

In the International ITI Study, a prospective randomized study comparing a high-dose (200 international units [IU]/kg/day) and a low-dose (50 IU/kg 3 times per week) FVIII regimen, subjects in the high-dose arm achieved a negative titer (median 4.6 months [interquartile range (IQR) 2.8 to 13.8] vs. 9.2 months [IQR 4.9 to 17.0]; p = 0.017) and a normal recovery (median 6.9 months [IQR 3.5 to 12.0] vs. 13.6 months [IQR 8.7 to 19.0]; p = 0.001) significantly more rapidly than subjects in the low-dose arm. High-dose subjects also experienced significantly fewer bleeding episodes than low-dose subjects, and for this reason, the data safety monitoring board recommended study termination (Hay & DiMichele, 2012).

These findings and limited experience in patients with hemophilia who have inhibitors have led to an interest in investigating the use of the Extended Half-Life (EHL) recombinant coagulation factor VIII Fc fusion protein (rFVIIIFc) in ITI. rFVIIIFc was approved in the United States of America (USA), Canada, and Japan in 2014 with the name of Eloctate and in Europe in 2015 with the name of Elocta.

Study Objectives and Endpoints:

Objectives

The primary objective of the study is to describe the time to tolerization (ITI success, i.e., inhibitor titer <0.6 BU/mL, rFVIIIFc incremental recovery [IR] ≥66% of the expected IR, and $t_{½}$ ≥7 hours) with rFVIIIFc in subjects within a maximum of 12 months (48 weeks) of ITI treatment.

The secondary objectives are as follows:

- To describe the outcome of ITI treatment
- To describe the relapse rate over the 48-week (12-month) period following successful ITI performed with rFVIIIFc
- To describe the intercurrent bleeding during the ITI Period and during the 48-week (12-month) period after successful ITI performed with rFVIIIFc
- To describe the safety and tolerability of rFVIIIFc when used for ITI
- To evaluate the impact of ITI treatment with rFVIIIFc on health economics and adherence

The exploratory objectives are as follows:

- [redacted]
- [redacted]

Endpoints

The primary endpoint of this study is time to tolerization with a maximum of 12 months (48 weeks) of ITI treatment offered in the study (tolerization defined as inhibitor titer <0.6 BU/mL, rFVIIIFc incremental recovery [IR] of ≥66% of expected, and half-life [$t_{½}$] of ≥7 hours).

The secondary endpoints are as follows:

- ITI success
  - Confirmed negative titers consisting of 2 consecutive negative inhibitor assessments within 2 weeks (±3 days) based on local laboratory results <0.6 BU/mL by the Nijmegen-modified Bethesda assay; determination of negative titer based on the Bethesda assay is acceptable at sites that have not yet adopted the Nijmegen-modified Bethesda assay.
  - IR ≥1.32 IU/dL per IU/kg in 2 consecutive assessments representing ≥66% of the expected IR 2 IU/dL per IU/kg.(SmPC; USPI)
  - $t_{½}$ ≥7 hours.
- Occurrence of relapse (defined as confirmed positive inhibitor titer ≥0.6 BU/mL), abnormal recovery after tolerance is achieved, and $t_{½}$ <7 hours) during the Tapering or Follow-Up Periods
- Number of bleeding episodes during the ITI Period and during the 48-week (12-month) period after successful ITI performed with rFVIIIFc
- Adverse events and serious adverse events
- Number of days away from work or school
- Number of hospitalization days
- Adherence (defined as percentage of administered doses

versus planned doses)

- Consumption of rFVIIIFc (measured in total rFVIIIFc use)

The exploratory endpoints are as follows:

[redacted]

The exploratory endpoint [redacted] will be reported outside the clinical study report.

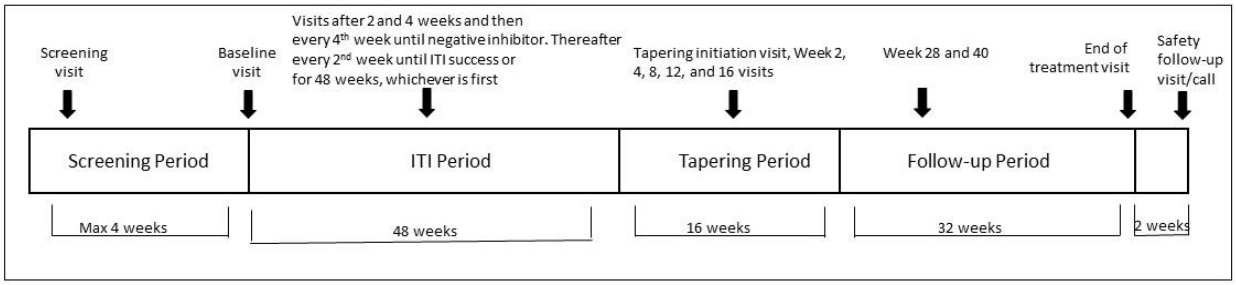
Study Design:	An open-label, single-arm, interventional, multicenter study designed to explore the use of rFVIIIFc for ITI in subjects with severe hemophilia A, who are undergoing ITI treatment for the first time. The study consists of 1) a 4-week (1-month) Screening Period; 2) a maximum of a 48-week (12-month) ITI Period; 3) a minimum of a 16-week (4-month) Tapering Period after all criteria for tolerization have been met; and 4) a 32-week (8-month) Follow-Up Period. Only subjects who achieve ITI success will enter the Tapering and Follow-Up Periods. During the Tapering and Follow-Up Periods, the subject's dose will be adjusted to achieve the prophylactic dose.
Study Location and Number of Sites:	Approximately 30 sites in the USA, Europe, Japan, and Canada
Number of Planned Subjects:	Up to 17 subjects
Study Population:	This study will be conducted in male subjects of any age with severe hemophilia A and high-titer inhibitors (historical peak ≥5 BU/mL), who have been previously treated with any plasma-derived FVIII or recombinant conventional or EHL FVIII and are undergoing ITI treatment for the first time.

	Detailed criteria are described in Section 8.
Treatment Groups:	This is a single-arm study that will enroll up to 17 subjects
Duration of Treatment and Follow-Up:	Study duration for each subject will vary based on time to ITI success. The maximum individual subject study duration is expected to be approximately 2 years.

4. STUDY SCHEMATIC AND SCHEDULE OF ACTIVITIES

4.1. Study Schematic

Figure 1: 997HA402 Study Design



Abbreviations: ITI=immune tolerance induction; Max=maximum.

Only subjects who achieve ITI success within the 48-week (12-month) ITI Period will continue into the Tapering and Follow-Up Periods. During the Tapering and Follow-Up Periods, the subject's dose will be adjusted to achieve the prophylactic dose. However, if FVIII peak activity levels rise above 200 IU/dL after the inhibitors are negative but before all the ITI success criteria are met, the dose may be adjusted according to Investigator judgment to maintain the FVIII peak activity levels between 100 and 200 IU/dL. This dose reduction will not be considered part of the Tapering Period, and the subject will maintain the schedule of assessments per the ITI Period. See Section 11.1 for dosing details.

4.2. Schedules of Activities

Table 1: **Schedule of Activities for Screening Visit and ITI Period**

Activities	**Screening Visit**	**ITI Period**				**EOT for Partial Success or Failure[1]**	
		Baseline Visit (within 4 weeks of Screening)	**Week 2 Visit**	**Interim ITI Visits**	**ITI Outcome Assessment Visit**	**EOT Visit**	**Final Safety Follow-Up**
		Start of ITI treatment	**2 weeks (±3 days) from start of ITI treatment**	**Every 4th week (±1 week) Starting at ITI Week 4 until first negative titer (<0.6 BU/mL) is achieved OR 48 weeks of ITI treatment[2]**	**Every 2nd week (±3 days) Starting at time of first negative inhibitor titer until ITI success OR 48 weeks of ITI treatment**		**7 to 14 days after EOT Visit**
Informed Consent or Assent Form	X						
Assessment of Subject Eligibility	X						
Demographics	X						
Medical, Surgical, Hemophilia, Inhibitor, Bleeding Episodes, and ITI History	X						
Physical Examination	X	X	X	X	X	X	
Height (cm)	X					X	
Weight (kg)	X	X	X	X	X	X	
Vital Signs[3]	X	X	X	X	X	X	

Activities	Screening Visit	ITI Period				EOT for Partial Success or Failure[1]	
		Baseline Visit (within 4 weeks of Screening)	Week 2 Visit	Interim ITI Visits	ITI Outcome Assessment Visit	EOT Visit	Final Safety Follow-Up
		Start of ITI treatment	2 weeks (±3 days) from start of ITI treatment	Every 4th week (±1 week) Starting at ITI Week 4 until first negative titer (<0.6 BU/mL) is achieved OR 48 weeks of ITI treatment[2]	Every 2nd week (±3 days) Starting at time of first negative inhibitor titer until ITI success OR 48 weeks of ITI treatment		7 to 14 days after EOT Visit
Hematology (Local Laboratory)[4]	X	X		X	X	X	
Blood Chemistry (Local Laboratory)[4]	X	X		X	X	X	
Urinalysis (Local Laboratory)[4,5]	X	X		X	X	X	
Viral Analysis (HIV, HCV, and HBV) (Central Laboratory)[6]	X						
Blood Sample for Analysis of FVIII Mutation and HLA Allotyping (Central Laboratory) (Optional)[7]		X					
rFVIIIFc Dosing[8]		X	X	X	X	X	

Activities	**Screening Visit**	**ITI Period**				**EOT for Partial Success or Failure[1]**	
		Baseline Visit (within 4 weeks of Screening)	**Week 2 Visit**	**Interim ITI Visits**	**ITI Outcome Assessment Visit**	**EOT Visit**	**Final Safety Follow-Up**
		Start of ITI treatment	**2 weeks (±3 days) from start of ITI treatment**	**Every 4th week (±1 week) Starting at ITI Week 4 until first negative titer (<0.6 BU/mL) is achieved OR 48 weeks of ITI treatment[2]**	**Every 2nd week (±3 days) Starting at time of first negative inhibitor titer until ITI success OR 48 weeks of ITI treatment**		**7 to 14 days after EOT Visit**
Nijmegen-Modified Bethesda Inhibitor Assay (Both Local and Central Laboratories)[9]	X	X	X		X	X	
Anti-rFVIIIFc Antibody (ADA) (Central Laboratories)[10]	X	X		X	X	X	
Blood Sample for Immune Cell Characterization (Central Laboratory)[11]		X		X		X	
FVIII Activity Level (Both Local and Central Laboratories)[12]			X	X	X	X	
FVIII Activity for IR (Both Local and Central Laboratories)[13]					X		

Activities	Screening Visit	ITI Period				EOT for Partial Success or Failure[1]	
		Baseline Visit (within 4 weeks of Screening)	Week 2 Visit	Interim ITI Visits	ITI Outcome Assessment Visit	EOT Visit	Final Safety Follow-Up
		Start of ITI treatment	2 weeks (±3 days) from start of ITI treatment	Every 4th week (±1 week) Starting at ITI Week 4 until first negative titer (<0.6 BU/mL) is achieved OR 48 weeks of ITI treatment[2]	Every 2nd week (±3 days) Starting at time of first negative inhibitor titer until ITI success OR 48 weeks of ITI treatment		7 to 14 days after EOT Visit
FVIII Activity for $t_{½}$ Evaluation (Both Local and Central Laboratory)[14]					X	X	
EPD Review, Including Review of Bleeding Episodes and rFVIIIFc Dosing Accountability[15]		X	X	X	X	X	
Nonserious Adverse Events		X	X	X	X	X	X
Serious Adverse Events[16]	X	X	X	X	X	X	X
Concomitant Therapy/Procedures Recording	X	X	X	X	X	X	X

Abbreviations: ADA=anti-drug antibody; BU=Bethesda Unit; EOT=end of treatment; EPD=electronic patient diary; FVIII=coagulation factor VIII; HBV=hepatitis B virus; HCV=hepatitis C virus; HIV=human immunodeficiency virus; HLA=human leukocyte antigen; ICF=informed consent form; IR=incremental recovery; ITI=immune tolerance induction; rFVIIIFc=recombinant coagulation factor VIII Fc fusion protein; $t_{½}$=half-life.
NOTE: inhibitor titer, FVIII activity level, $t_{½}$, and IR are all assessed at the local laboratory, with confirmation by the central laboratory. The Investigators will use local laboratory results for decision-making purposes. Hematology, blood chemistry, and urinalysis are assessed only at the local laboratory.

[1] Subject will be allowed to get the confirmatory test, even if it is after the 48-week (12-month) period, as long as the first test occurred during the 48-week (12-month) period. If the second test confirms the results of the first test (<0.6 BU/mL), the date of ITI outcome will be the date of the first value, which occurred during the 48-week (12-month) period. Fluctuations in inhibitor levels is common and variability in inhibitor titer is expected. Subjects will be treated on a case-by-case basis.

[2] If, after the initial 3 months (12 weeks), there is no downward trend (at least 20% in the inhibitor titer) over a 6-month (24-week) period that is assessed at the Week 36 interim ITI Visit, the subject will be considered a treatment failure and must complete the EOT Visit as soon as possible. The second (confirmatory) inhibitor test will occur 2 weeks after the first negative inhibitor test.

[3] Vital signs include blood pressure, pulse rate, respiratory rate, and body temperature. In the event of in-clinic rFVIIIFc injections, assessments will be taken prior to and 20 (±5) minutes after the end of the rFVIIIFc injection (if dosing occurs at the visit).

[4] Blood samples for determination of hematology and blood chemistry variables and urine dipstick will be collected at Screening Visit, Baseline Visit (before the first study treatment administration), and then every 12 weeks (3 months) from the start of the ITI Period through the time of ITI complete success. If the subject completes the ITI Period in a duration shorter than 12 weeks (3 months), these assessments must be completed at the end of the ITI Period.

[5] Dipstick urinalysis, including a protein reading; if the protein reading is positive (≥1+), a full laboratory urinalysis will be required.

[6] Sample will be collected and tested if there are no HIV testing results available in the medical history 26 weeks (6.5 months) prior to Screening. HCV and HBV will only be tested at Screening if there is any indication in the medical record that the subject has prior exposure to plasma-derived coagulation factors. For subjects without prior exposure, the sample will be collected and stored at the central laboratory. If the subject is diagnosed with HBV or HCV during the study, this sample will be analyzed by the central laboratory to determine seropositivity at Screening.

[7] This assessment is optional, and requires a separate ICF. For subjects whose FVIII mutation and human leukocyte antigen (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 at any subsequent visit if blood volume is limited at the Baseline Visit for analysis at the central laboratory.
For Canada specific requirements: see Appendix B.

[8] Clinic dosing is applicable only if warranted.

[9] Subjects will be advised to delay administration of their daily dose of rFVIIIFc until after the sample for inhibitor testing is taken. For sites that have not yet adopted the Nijmegen-Modified Bethesda Assay, use of the Bethesda Assay is acceptable.

[10] A whole blood sample will be collected at Baseline OR Screening, every fourth week during interim ITI Visits, during assessment of ITI outcome visits, and at EOT. A sample for Anti-rFVIIIFc Antibody (ADA) should be collected at Baseline or Screening, and each consecutive visit, except the Week 2 and Safety Follow-Up Visits when allowed by the total volume of plasma that can be collected in one day.

[11] A whole blood sample will be collected at ITI Day 1 (Baseline Visit, predose) and at Week 8 (Month 2), as allowable based on subject weight and institutional practice regarding blood draw restrictions for pediatric subjects.

[12] A sample for FVIII activity will be collected at visits where samples for IR or t½ assessments are not collected.

[13] IR assessment will only be performed after a negative inhibitor has been confirmed at 2 consecutive visits. The sample for IR is drawn at the visit for the confirmatory negative inhibitor titer. However, the interpretation of the IR result will be performed after the negative inhibitor titer is confirmed. The predose sample for IR calculations is to be taken when the subject is in a nonbleeding state and after at least a 24-hour washout. See Table 3 for details.
Subjects will be advised to delay administration of their daily dose of rFVIIIFc until after the sample for IR testing is taken

[14] Subjects will be advised to delay administration of their daily dose of rFVIIIFc until after the sample for t½ is taken. Half-life determination will only be performed after IR ≥1.32 IU/dL per IU/kg has been confirmed at 2 consecutive visits or as part of the EOT Visit. t½ determinations are to be performed

when the subject is in a nonbleeding state and after at least a 24-hour washout. t½ determination at EOT Visit does not need to be performed if the full 4-sample t½ assessment was performed within 2 weeks prior to the EOT Visit or if the Investigator determines the subject is an ITI Treatment Failure.

[15] It is recommended that subjects/caregivers enter dosing information immediately after an injection or within a maximum of 7 days.

[16] Serious adverse events are to be monitored and recorded from the time of signing of the ICF.

Table 2: Schedule of Activities for the Tapering and Follow-Up Periods After Successful Tolerization

Activities	Tapering Period[1]	Follow-Up Period[1]	EOT[2]	
	Tapering Initiation Visit/Telephone Call,[3] Week 2, 4, 8, 12, and 16 Visits	Week 28 and 40 Visits[4]	EOT Visit	Final Safety Follow-Up
	Starting at ITI success and continuing for a minimum of 16 weeks with visits after 2 weeks (±3 days), 4 weeks (±1 week), and then every 4th week (±1 week)	Week 28 and 40 visits (±2 weeks)[1] following ITI success	Week 48 visit (±2 weeks) following ITI success OR upon relapse	7 to 14 days after EOT Visit
Physical Examination	X	X	X	
Height (cm)			X	
Weight (kg)	X	X	X	
Vital Signs[5]	X	X	X	
Hematology (Local Laboratory) [6,]	X		X	
Blood Chemistry (Local Laboratory)[6]	X		X	
Urinalysis (Local Laboratory)[6,7]	X		X	
Nijmegen-Modified Bethesda Inhibitor Assay (Both Local and Central Laboratories)[8]	X	X	X	
Anti-rFVIIIFc Antibody (ADA) (Central Laboratory)	X	X	X	

Activities	Tapering Period[1]	Follow-Up Period[1]	EOT[2]	
	Tapering Initiation Visit/Telephone Call,[3] Week 2, 4, 8, 12, and 16 Visits	Week 28 and 40 Visits[4]	EOT Visit	Final Safety Follow-Up
	Starting at ITI success and continuing for a minimum of 16 weeks with visits after 2 weeks (±3 days), 4 weeks (±1 week), and then every 4th week (±1 week)	Week 28 and 40 visits (±2 weeks)[1] following ITI success	Week 48 visit (±2 weeks) following ITI success OR upon relapse	7 to 14 days after EOT Visit
Blood Sample for Immune Cell Characterization (Required) (Central Laboratory)[9]	X		X	
rFVIIIFc Dosing[10]	X	X	X	
FVIII Activity for IR (Both Local and Central Laboratories)[11]	X	X		
FVIII Activity for $t_{½}$ Evaluation (Both Local and Central Laboratories)[12]			X	
FVIII Activity Level (Both Local and Central Laboratories)[13]		X	X	
EPD Review, Including Review of Bleeding Episodes and rFVIIIFc Dosing Accountability[14]	X	X	X	
Nonserious Adverse Events	X	X	X	X
Serious Adverse Events	X	X	X	X

Activities	Tapering Period[1]	Follow-Up Period[1]	EOT[2]	
	Tapering Initiation Visit/Telephone Call,[3] Week 2, 4, 8, 12, and 16 Visits	Week 28 and 40 Visits[4]	EOT Visit	Final Safety Follow-Up
	Starting at ITI success and continuing for a minimum of 16 weeks with visits after 2 weeks (±3 days), 4 weeks (±1 week), and then every 4th week (±1 week)	Week 28 and 40 visits (±2 weeks)[1] following ITI success	Week 48 visit (±2 weeks) following ITI success OR upon relapse	7 to 14 days after EOT Visit
Concomitant Therapy/ Procedures Recording	X	X	X	X

Abbreviations: EOT=End of Treatment; EPD=electronic patient diary; ET=early termination; FVIII=coagulation factor VIII; IR=incremental recovery; ITI=immune tolerance induction; PK=pharmacokinetic; rFVIIIFc=recombinant coagulation factor VIII Fc fusion protein; t½=half-life.
NOTE: inhibitor titer, FVIII activity level, t½, and IR are all assessed at the local laboratory, with confirmation by the central laboratory. The Investigators will use local laboratory results for decision-making purposes.
Hematology, blood chemistry, and urinalysis are assessed only at the local laboratory.

1 During the Tapering and Follow-Up Periods, the subject's dose will be adjusted to achieve each subject's prophylactic dose as determined by the Investigator. Minimum Tapering Period is 16 weeks (4 months). Subjects who relapse during the Tapering Period (i.e., who have confirmation of inhibitor development AND who have confirmed decrease of IR, with or without clinical signs or symptoms) will proceed immediately to the EOT Visit. Subjects will be closely monitored during the Tapering Period for potential relapse.
For Canada specific requirements: see Appendix B.

2 Timing of the EOT Visit will vary for subjects, as described in Section 7.2.6.

3 Once t½ has been determined to be ≥7 hours, the Investigator may elect to have a Tapering Initiation Visit and/or a Tapering Initiation Telephone Call. If the subject has already begun downtitration from the 200 IU/kg/day ITI dose prior to ITI success, the subject will return for the next scheduled visit (the Tapering Initiation Visit) 2 weeks from the visit at which t½ was determined to be ≥7 hours. If the subject has not already downtitrated when t½ is determined to be ≥7 hours, the Investigator can make a telephone call to instruct the subject to begin downtitrating immediately (Tapering Initiation Telephone Call) Subject's subsequent visit, which will occur 2 weeks from the visit at which t½ was determined to be ≥7 hours, will be the Tapering Initiation Visit (see Section 7.2.3).

4 Subjects who do not achieve ITI success within 48 weeks (12 months) will proceed to the ET/EOT Visit. Subjects who develop inhibitors during the Tapering or the Follow-Up Period (i.e., who relapse) will proceed immediately to the ET/EOT Visit.

5 Vital signs include blood pressure, pulse rate, respiratory rate, and body temperature. Postdose assessments following in-clinic injections will be taken prior to and 20 (±5) minutes after the end of the rFVIIIFc injection (if dosing occurs at the visit).

6 Hematology, blood chemistry, and urine dipstick are to be collected every 12 weeks (3 months) during the Tapering Period. These assessments will also be collected at the EOT Visit.

7 Dipstick urinalysis, including a protein reading; if the protein reading is positive (≥1+), a full laboratory urinalysis will be required.

8 Subjects will be advised to delay administration of their daily dose of rFVIIIFc until after the sample for inhibitor testing is taken. An unscheduled visit may be required to repeat inhibitor testing under this protocol to obtain a sample to confirm a positive inhibitor test result.
9 If ITI success is declared, a sample will be collected at the first visit in the Tapering Period. If partial success or failure is declared, a sample will be collected at the EOT Visit. The samples will be collected as allowable based on subject weight and institutional practice regarding blood draw restrictions for pediatric subjects.
10 Takes place at each visit in which IR or $t_{½}$ is being assessed.
11 Subjects will be advised to delay administration of the remainder of their daily dose of rFVIIIFc until after the sample for IR is taken. Blood samples will be collected for analysis of rFVIIIFc activity for assessment of IR starting at the visit for confirmed negative titers and at all consecutive visits, except for those visits where samples for rFVIIIFc t½ determination are drawn, as IR will be determined from the same samples. Blood samples will be taken at predose (within 30 minutes prior to the start of injection) and postdose (30 ± 5 minutes after the start of injection). If any assessments indicate the possibility of relapse at any time during the Tapering or Follow-Up Period, the test must be repeated at the following visit to confirm relapse (i.e., IR <66%).
12 Subjects will be advised to delay administration of the remainder of their daily dose of rFVIIIFc until after the final post-dose sample for $t_{½}$ is taken (i.e., up to 48 hours post dose). PK assessments for $t_{½}$ determination are to be performed when the subject is in a nonbleeding state and after at least a 24-hour washout (see Table 3).
13 A sample for FVIII activity can be collected as needed per Investigator discretion. FVIII activity levels can be derived from IR samples; therefore, a separate blood draw for FVIII activity assessment is not required.
14 It is recommended that subjects/caregivers enter dosing information immediately after an injection or within a maximum of 7 days.

Details on sampling for rFVIIIFc are described in Section 13.1.3 and Table 3.

Table 3: Sampling Schedule for Pharmacokinetic Evaluation (Half-Life)

Activities	Time in Relation to rFVIIIFc Dosing						
		rFVIIIFc Dosing 50 IU/kg Actual Potency	**First Sample Postdose**	**Second Sample Postdose**	**Third Sample Postdose**[1]	**Fourth Sample Postdose Either 30 h OR 48 h Sample**	
	Predose[2]	**0**	**30 min (±5 min)**	**6 h (±10 min)**	**24 h (±60 min)**	**30 h (±60 min)**	**48 h (±60 min)**
rFVIIIFc Dosing		X					
PK Assessments[2] [3]	X		X	X	X	X	X

Abbreviations: h=hours; min=minutes; PK=pharmacokinetic; rFVIIIFc=recombinant coagulation factor VIII Fc fusion protein.

NOTE:$t_{½}$ assessment will also be performed at EOT for all subjects, unless all 4 postdose PK samples (as above) were assessed within 2 weeks of EOT or, in the case of subjects who fail ITI treatment.

[1] During the ITI Period, the Investigator may forego the fourth PK sample (i.e., the 30- or 48-hour sample), if, in the Investigator's opinion, the $t_{½}$ at the third PK sample indicates that a $t_{½} \geq 7$ hours cannot be achieved. In this case, the Investigator will document the decision to forego the fourth sample.

[2] Predose sample is to be collected within 30 minutes prior to the start of the rFVIIIFc injection.

[3] Timepoints for PK assessment are measured from the start of the factor injection.

5. INTRODUCTION

In this study, male subjects of all ages with severe hemophilia A and high-titer inhibitors (historical peak ≥5 Bethesda Unit [BU]/mL) will receive recombinant coagulation factor VIII Fc fusion protein (rFVIIIFc) for first-time immune tolerance induction (ITI) therapy, to eradicate and neutralize anti-coagulation factor VIII (FVIII) alloantibodies (inhibitors).

5.1. Overview of Immune Tolerance Induction in the Clinical Management of Hemophilia A

Hemophilia A is a rare X-linked bleeding disorder that is caused by a functional deficiency of FVIII, a cofactor in the intrinsic coagulation pathway. Hemophilia A is the most common type of hemophilia and is categorized based on endogenous FVIII activity levels as severe (<1 international units [IU]/dL), moderate (1 to 5 IU/dL), and mild (>5 to <40 IU/dL) (ISTH Factor VIII/IX Scientific Subcommittee (SSC) Working Party on Definitions in Hemophilia, 2011; Srivastava et al., 2012; White et al., 2001). As there is no available cure for hemophilia A, current treatment focuses on replacement therapy with clotting factor concentrates, namely plasma-derived FVIII (pdFVIII) or recombinant factor VIII (rFVIII) products.

The formation of neutralizing anti-FVIII alloantibodies (inhibitors) represents the most serious complication related to hemophilia treatment (Kempton et al., 2014). Inhibitors are immunoglobulin G antibodies formed against specific epitopes of the FVIII molecule, which can neutralize the coagulation activity of FVIII in plasma and reduce the recovery and half-life ($t_{½}$) of FVIII. Inhibitors result in rapid clearance of infused FVIII and marked reduction, or absence, of efficacy of FVIII treatment. Approximately 30% of previously untreated patients with severe hemophilia A develop inhibitors following exposure to replacement FVIII (Franchini et al., 2013; Gouw et al., 2013). The presence of an inhibitor 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 (Scalone et al., 2006). Patients with inhibitors also have a higher risk of mortality due to bleeding complications (Walsh et al., 2015).

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 (Caram et al., 2011; Tagariello et al., 2013). 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 (Tagariello et al., 2013), 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 (Caram et al., 2011), suggesting that a titer of ≥10 BU/mL is a better predictor for a persistent inhibitor.

In patients with low-titer inhibitors, bleeding episodes may be controlled with increased doses of replacement FVIII to overwhelm the inhibitor by antigen excess. In patients with high-titer

inhibitors, bleeding episodes are often treated with bypassing agents (activated prothrombin complex concentrate [aPCC], FEIBA®, factor eight inhibitor bypassing activity] or recombinant activated factor VII [rFVIIa, NovoSeven®]), which can bypass FVIII inhibition, but inhibitor eradication remains the goal of long-term management (see Section 7.2.2.1).

To date, ITI therapy using frequent administration of high doses of FVIII is the only proven strategy to achieve antigen-specific tolerance and eradicate FVIII inhibitors. 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 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 $t_{½}$, and elimination of the anamnestic response to FVIII challenge (Kempton et al., 2014; Valentino et al., 2015). ITI success rates range from 33% to 88% in published studies (Coppola et al., 2009; Dimichele, 2009; Gringeri, 2007; Hay & DiMichele, 2012; Haya et al., 2001; Jimenez-Yuste et al., 2016; Kreuz, Escuriola Ettingshausen, Vdovin, Zozulya, Plyushch, Svirin, Andreeva, Bubanská, et al., 2016; Kurth et al., 2011; Nakar et al., 2015; Oldenburg et al., 2014). Most ITI studies with reported success rates are based on retrospective registries or analyses, which may have limitations with the types of data collected. The wide variability in success rates can be attributed to numerous factors, including differences in FVIII product types and dosing regimens, patient characteristics, and definitions of success and methods for calculating success rates across ITI studies.

Over the last 30 years, multiple ITI regimens have been developed, and all involve frequent, often daily, repetitive exposure to FVIII for months or years. ITI usually attempts to eliminate high-responding FVIII inhibitors (≥5 BU/mL titer). ITI regimens employ different doses and dosing frequencies of FVIII, and they may or may not involve adjunctive immunomodulatory therapy (Franchini et al., 2011; Valentino et al., 2015). Currently, a range of FVIII products and dosing regimens are used for ITI because there is no clear consensus on an optimal regimen (Franchini et al., 2011). In the only prospective randomized ITI study ever conducted (International ITI Study) comparing a high-dose (200 IU/kg/day) and a low-dose (50 IU/kg 3 times per week) FVIII regimen, subjects in the high-dose arm achieved a negative titer (median 4.6 months [interquartile range (IQR) 2.8 to 13.8] vs. 9.2 months [IQR 4.9 to 17.0]; $p = 0.017$) and a normal recovery (median 6.9 months (IQR 3.5 to 12.0) vs. 13.6 months (IQR 8.7 to 19.0); $p = 0.001$) significantly more rapidly than subjects in the low-dose arm. High-dose subjects also experienced significantly fewer bleeding episodes than low-dose subjects, and for this reason, the data safety monitoring board recommended study termination (Hay & DiMichele, 2012). Although it is recommended that ITI be initiated once an inhibitor titer is <10 BU/mL (Valentino et al., 2015), a recent study suggests that starting ITI as soon as an inhibitor is diagnosed may increase the likelihood of ITI success (Nakar et al., 2015).

Factors that can affect ITI success have been identified in ITI studies. In particular, certain patient characteristics, including 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 (Gringeri, 2007; Hay & DiMichele, 2012; Kreuz, Escuriola Ettingshausen, Vdovin, Zozulya, Plyushch, Svirin, Andreeva, Bubanská, et al.,

2016; Valentino et al., 2015). For example, a statistically significant inverse relationship between historical peak inhibitor titer and ITI success was observed in the International ITI Registry (IITR; p = 0.004) and North American ITI Registry (NAITR; p = 0.001) (DiMichele et al., 2002; Mariani et al., 1994). Immune tolerance was achieved in 82% of patients whose historical peak inhibitor titer was <50 BU/mL, compared with 52% and 21% of patients whose historical peak inhibitor titer was >200 BU/mL in the IITR and NAITR, respectively (Kroner, 1999). In addition, a statistically significant association between inhibitor titer at ITI start (≤10 BU/mL vs. >10 BU/mL) and ITI outcome (p = 0.0068) was observed in the Observational ITI Study (Kreuz, Escuriola Ettingshausen, Vdovin, Zozulya, Plyushch, Svirin, Andreeva, Bubanská, et al., 2016), and an inhibitor titer <10 BU mL at ITI start was the strongest predictor of ITI success in the IITR (80% vs. 60%; p < 0.002), NAITR (83% vs 40%; p = 0.001), and a retrospective survey of 81 patients in the United States (100% vs 78%; p < 0.0001) (Damiano et al., 2000; DiMichele et al., 2002; Mariani et al., 1994).

Reported success rates can reflect different methods for calculation. For example, in the International ITI Study, a prospective study conducted in patients without high-risk factors, the success rate was 40% (46/115) for all subjects, 47% (37/78) for subjects who completed or withdrew from the study, and 70% (46/66) when subjects who were ongoing or withdrawn were excluded (Hay & DiMichele, 2012).

Additional prospective studies are needed to better understand ITI success rates. To date, there are few anecdotal case reports that describe the use of rFVIIIFc for the treatment of ITI. This prospective study is aimed at assessing the outcomes of ITI therapy with the use of rFVIIIFc.

5.2. Profile of Previous Experience With rFVIIIFc for Immune Tolerance Induction

5.2.1. Previous Nonclinical and Clinical Experience With rFVIIIFc for Immune Tolerance Induction

rFVIIIFc is produced in a human cell line (HEK293) as a recombinant B-domain deleted 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, nonhuman 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 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 (Lissitchkov et al., 2015).

5.2.2. Nonclinical Experience

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 (Lei et al., 2005). 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 (Gupta et al., 2015). 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 (Krishnamoorthy et al., 2016). 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.

5.2.3. Clinical Experience

In the clinical setting, there are published case reports of patients who have received rFVIIIFc for ITI. Malec and coworkers described 3 patients with severe hemophilia A (ages at initiation of ITI were 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 to 200 IU/kg rFVIIIFc with a dosing interval of every other day to 3 times per week. ITI led to a negative inhibitor in all 3 children within 4 to 12 weeks (Malec et al., 2015) , which is shorter than the median time to negative inhibitor reported for other FVIII products (Hay, DiMichele, et al., 2012; Kreuz, Escuriola Ettingshausen, Vdovin, Zozulya, Plyushch, Svirin, Andreeva, Bubanska, et al., 2016). Malec and coworkers reported the time to tolerization in these 3 patients being 17 weeks, 18 weeks, and 17 months, respectively (Carcao et al., 2017; Malec et al., 2016). Groomes and coworkers reported a 15-month-old patient who started ITI on conventional rFVIII products. As the inhibitor titer continued to increase, he was switched to rFVIIIFc 50 IU/kg 3 times per week. The inhibitor titer had significantly decreased to 0.7 BU/mL after 10 months of ITI at the time of publication (Groomes et al., 2016).

5.3. Study Rationale

Hemophilia management has advanced rapidly in the last few years. Formation of inhibitors still remains the main complication of treatment of hemophilia. ITI is the standard of care for treatment of inhibitor development for patients with hemophilia A; however, there remains an unmet need for a standard dose and a specific product to treat these inhibitors. A range of FVIII products and dosing regimens have been studied in a number of generally small retrospective registries and 1 prospective study. ITI success rates from these studies range from 33% to 88%, due in part to the widely varying definitions of success, FVIII product types used, dose regimens, and study populations. The International ITI Study was the only prospective study performed to date (Hay & DiMichele, 2012). This study evaluated high-dose (200 IU/kg/day) and low-dose (50 IU/kg 3 times per week) ITI regimens in subjects without risk factors associated with poor

ITI outcomes. Of the 57 subjects who received high-dose ITI with FVIII, 22 (39%) achieved complete success. Based on the results of this study and several registries, Valentino (Valentino et al., 2015) published recommendations on ITI treatment. However, there is no clear consensus on an optimal regimen, making additional prospective studies necessary.

Furthermore, rFVIIIFc offers a potential advantage over other replacement FVIII products for treating patients with hemophilia A and inhibitors. Based on reports from animal studies, Fc-containing fusion proteins have immunomodulatory properties, which may be attributable to the ability to upregulate regulatory T cells via epitopes present in the Fc fragment (De Groot et al., 2008) and consequently promote tolerance over immune responses that induce immunogenicity. These and other nonclinical data (Krishnamoorthy et al., 2016) indicate a mechanistic basis for the use of rFVIIIFc for ITI, and promising clinical results from published reports (Groomes et al., 2016; Malec et al., 2015) provide initial evidence that rFVIIIFc can induce tolerance.

5.4. Rationale for Dosing Regimen

The proposed dose of rFVIIIFc for ITI (200 IU/kg/day [±8 hours]) is aligned with current ITI guidelines (Valentino et al., 2015). Since clearance is expected to be very rapid in the presence of inhibitors irrespective of the type of FVIII product, the high dose of 200 IU/kg/day evaluated in the International ITI Study will be used in the present study to achieve faster tolerization with fewer bleeding episodes. This dosing regimen is also supported by the results of a prospective clinical study that compared subjects treated with FVIII for ITI at a high dose (200 IU/kg/day) and a low dose (50 IU/kg 3 times per week). Results from this study (Hay & DiMichele, 2012) demonstrated that the times to achieve negative inhibitor titer, normal FVIII recovery, and FVIII tolerance were shorter in subjects treated with the high dose of FVIII compared with subjects treated with the low dose. Furthermore, subjects treated with the high dose of FVIII for ITI had a lower rate of intercurrent bleeding and fewer hospitalizations due to bleeding than subjects treated with the low dose of FVIII. Anecdotal unpublished reports of cases treated in the United States of America (USA) and Canada with 200 IU/kg/day also exist.

Furthermore, repeated doses of up to 1000 IU/kg evaluated in the nonclinical animal studies have shown no dose-limiting toxicities.

Sustained high FVIII activity levels in plasma (>150 to 200 IU/dL) may increase the risk of thrombotic events, although this risk is thought to be low. Therefore, FVIII activity levels in plasma will be monitored to provide a basis for dose adjustment of rFVIIIFc when needed. During the Tapering and Follow-Up Periods, the subject's dose will be adjusted to achieve a prophylactic dose (see Section 11.1).

6. STUDY OBJECTIVES AND ENDPOINTS

6.1. Primary Objective and Endpoint

The primary objective of this study is to describe the time to tolerization (i.e., ITI success) with rFVIIIFc in subjects within a maximum of 48 weeks (12 months) of ITI treatment.

The primary endpoint of this study is time to tolerization with a maximum of 48 weeks (12 months) of ITI treatment offered in the study (tolerization defined as inhibitor titer <0.6 BU/mL, rFVIIIFc incremental recovery [IR] ≥66% of the expected IR, and $t_{½}$ ≥7 hours).

6.2. Secondary Objectives and Endpoints

The secondary objectives are as follows:

- To describe the outcome of ITI treatment
- To describe the relapse rate over the 48-week (12-month) period following successful ITI performed with rFVIIIFc
- To describe the intercurrent bleeding during the ITI Period and during the 48-week (12-month) period after successful ITI performed with rFVIIIFc
- To describe the safety and tolerability of rFVIIIFc when used for ITI
- To evaluate the impact of ITI treatment with rFVIIIFc on health economics and adherence

The secondary endpoints are as follows:

- ITI success
  - Confirmed negative titers consisting of 2 consecutive negative inhibitor assessments within 2 weeks (±3 days) based on local laboratory results <0.6 BU/mL by the Nijmegen-modified Bethesda assay; determination of negative titer based on the Bethesda assay is acceptable at sites that have not yet adopted the Nijmegen-modified Bethesda assay
  - IR ≥1.32 IU/dL per IU/kg in 2 consecutive assessments representing ≥66% of the expected IR 2 IU/dL per IU/kg (SmPC; USPI)
  - $t_{½}$ ≥7 hours
- Occurrence of relapse (defined as confirmed positive inhibitor titer ≥0.6 BU/mL), abnormal recovery after tolerance is achieved, and $t_{½}$ <7 hours) during the Tapering or Follow-Up Periods
- Number of bleeding episodes during the ITI Period and during the 48-week (12-month) period after successful ITI performed with rFVIIIFc
- Adverse events (AEs) and serious adverse events (SAEs)

- Number of days away from work or school
- Number of hospitalization days
- Adherence (defined as percentage of administered doses versus planned doses)
- Consumption of rFVIIIFc (measured in total rFVIIIFc use)

6.3. Exploratory Objectives and Endpoints

7. STUDY DESIGN

7.1. Study Overview

This is an open-label, single-arm, interventional, multicenter study designed to explore the use of rFVIIIFc for ITI in subjects with severe hemophilia A who have inhibitors, who are undergoing ITI treatment for the first time. The study will be conducted at approximately 30 sites in the USA, Europe, Japan, and Canada. Approximately 17 subjects will be treated. The maximum individual subject study duration is expected to be approximately 2 years (see Figure 1 for a schematic of the study design).

7.2. Overall Study Duration and Follow-Up

The study period will consist of 4 periods: 1) a 4-week (1-month) Screening Period; 2) a maximum of a 48-week (12-month) ITI Period; 3) a minimum of a 16-week (4-month) Tapering Period after all criteria for tolerization have been met; and 4) a 32-week (8-month) Follow-Up Period. The length and the dosing schedules during the Tapering Period are left to the discretion of the treating physician. Only subjects who achieve ITI success will enter the Tapering and Follow-Up Periods. During the Tapering and Follow-Up Periods, the subject's dose will be adjusted with the aim of tapering the dose to reach the prophylactic dosing regimen within at least 12 weeks (3 months) (see Table 5).

7.2.1. Screening

Subjects will undergo full evaluation to determine their eligibility to participate in the study, after the subject or the subject's legally authorized representative (e.g., parent or legal guardian), as applicable, in accordance with local practice and regulations, has signed the informed consent form (ICF) (and assent, if applicable). Pediatric subjects who have the capacity should provide their assent to participate in the study.

Subject eligibility for the study will be determined within 4 weeks (1 month) prior to study entry, with the exception of informed consent, which may occur earlier. Subjects may be given a screening window extension of up to 2 weeks if unable to enroll within the 4-week (1 month) Screening Period. Screening laboratory results are valid for up to 6 weeks. Screen failures will be allowed to re-screen on a case-by-case basis and will require approval of the Sponsor Medical Monitor. Subjects weighing <6 kg may require Screening blood draws over multiple days to comply with the maximum allowable blood draw volumes. Alternatively, individual Investigators may choose to collect all Screening samples using a single blood draw after weighing the risk associated with multiple venipuncture attempts versus that of drawing all required samples at a single time. If the option of a single blood draw is chosen, the Investigator must document the rationale.

Subjects who meet all entry criteria will be enrolled and begin treatment at the Baseline Visit (see Table 1). A subject will be considered enrolled when the Investigator determines that the subject is eligible, and the subject is enrolled in the Interactive Response System (IXRS). Subject enrollment in IXRS must occur prior to dispensation of study treatment.

7.2.2. Immune Tolerance Induction Period

The first dose of rFVIIIFc ITI will be administered at the Baseline Visit, and treatment will continue until ITI success is declared or for a maximum of 48 weeks (12 months). The ITI regimen consists of rFVIIIFc 200 IU/kg/day (±8 hours), which may be given as once-daily injections or divided into several injections per day at the discretion of the Investigator.

Subjects will visit the clinic 2 and 4 weeks after enrollment and then every fourth week until 48 weeks (12 months) or until a negative inhibitor (<0.6 BU/mL) has been obtained. After the negative inhibitor results, visits will be scheduled every other week until ITI success or failure is declared.

The Investigator's assessment of ITI outcome will be based on results from the local laboratory. If the local laboratory results are inconclusive, the Investigator may use the central laboratory results to determine ITI outcome. During the ITI Period, subjects will undergo procedures and assessments at designated visits per Table 1. Samples for inhibitor testing and assessment of FVIII activity levels will be analyzed at the local laboratory and at the central laboratory. Investigator treatment and assessment of inhibitor status will be based on results from the local laboratory. Negative inhibitor testing results must be confirmed (i.e., 2 consistent results at 2 consecutive assessments). See Section 7.2.2.2 for specific definitions of ITI outcomes.

The assessment of ITI outcome is illustrated in Figure 2. After the subject has demonstrated a negative inhibitor (<0.6 BU/mL) at 2 consecutive assessments within 2 weeks (±3 days) per the schedule listed in Table 1, an evaluation of rFVIIIFc IR will be performed at the next scheduled visit (the interpretation of the IR result will be performed after the negative inhibitor titer is confirmed, but the sample for IR is drawn at the visit for the confirmatory negative inhibitor titer). After IR ≥1.32 IU/dL per IU/kg (≥66% of the expected IR) has been obtained at 2 consecutive assessments within 2 weeks (±3 days), together with a sustained negative inhibitor titer (<0.6 BU/mL), PK assessments to determine rFVIIIFc $t_{½}$ will be performed at the subsequent visits until $t_{½}$ ≥7 hours is attained. If $t_{½}$ <7 hours is attained, subjects need to return to clinic within 2 weeks (±3 days) to complete another $t_{½}$ assessment until ITI success or 48 weeks (12 months).

Subjects are required to have at least a 24-hour washout prior to the IR and the PK assessment for $t_{½}$. The dose for IR and $t_{½}$ is 50 IU/kg of rFVIIIFc based on actual potency. Investigators will advise subjects to delay any dose of rFVIIIFc until after scheduled inhibitor assessments. Investigators will also advise subjects to delay the remainder of their daily dose of rFVIIIFc until after IR and $t_{½}$ assessments have been made.

Only subjects who achieve confirmed ITI success within 48 weeks (12 months) will continue into the Tapering and Follow-Up Periods. Throughout the study, FVIII activity levels above 200 IU/dL (based on local laboratory values) should be avoided. However, if FVIII activity levels rise above 200 IU/dL after the inhibitors are negative but before all of the ITI success criteria are met, the dose may be adjusted according to Investigator judgment to maintain the FVIII activity levels between 100 and 200 IU/dL. This dose reduction will not be considered part of the Tapering Period, and the subject will maintain the schedule of assessments per the ITI Period. See Section 11.1 for dosing details.

Throughout the ITI Period, rFVIIIFc administration, bypassing agent administration, and any bleeding episodes will be collected by the subject and/or his caregiver in a study-specific electronic patient diary (EPD). EPD data will be reviewed by the Investigator on an ongoing basis and discussed with the subject at each visit.

7.2.2.1. Use of Bypassing Agents

In the time period between the subject's signing the ICF and the beginning of ITI treatment, treatment with bypassing agents (aPCC [FEIBA] or rFVIIa [NovoSeven]) is permitted.

During ITI treatment, subjects may also receive bypassing agents as needed for control of active bleeding at the discretion of the Investigator and within labeled dosing recommendations for the specific bypassing agent.

The Investigator may also prescribe bypassing agents if there is a high clinical suspicion of bleeding or potential for bleeding. When possible, bleeding should be confirmed via physical examination and/or imaging prior to administration of a bypassing agent; Confirmation of bleeding should not cause any unnecessary delay in the start of treatment, as judged by the Investigator.

In the event of an emergency, prior consultation with the Investigator is not required before administration of a bypassing agent; however, the Investigator must be notified of such use.

The use of bypassing agents in the setting of ITI requires awareness of FVIII activity levels and close monitoring for cessation of bleeding events.

In subjects with high-titer inhibitors, bleeding may be treated with bypassing agents, which can bypass FVIII inhibition. In subjects with low-titer inhibitors, bleeding events may be controlled with increased doses of replacement FVIII to overwhelm the inhibitor by antigen excess.

During the study, the Investigator will determine if increased doses of replacement FVIII or use of bypassing agents is appropriate.

It is recommended that Investigators discontinue the use of bypassing agents once the inhibitor titer is <0.6 BU/mL (negative titer, or values considered negative per local laboratory reference) or once rFVIIIFc provides sufficient hemostatic control, as judged by the Investigator.

The prophylactic use of bypassing agents in subjects with confirmed or suspected inhibitors is permitted; however, the Investigator must inform the Sponsor Medical Monitor and document the rationale for such use.

Throughout the ITI Period, rFVIIIFc administration, bypassing agent administration, and any bleeding episodes will be collected by the subject and/or his caregiver in a study-specific EPD.

EPD data will be reviewed by the Investigator in an ongoing basis and discussed with the subject at each visit.

7.2.2.2. ITI Outcome

ITI outcome will be assessed on an ongoing basis. Subjects may achieve 1 of 4 outcomes: treatment failure, early withdrawal (outcome not determinable) during the ITI Period, partial success, or ITI success.

Early withdrawal (Outcome not determinable)

- Unable to determine outcome due to withdrawal during the ITI Period

Treatment failure

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

- No downward trend of at least 20% in the inhibitor titer in a 6-month (24-week) period after the initial 3 months (12 weeks) during the ITI Period (assessed at the Week 36 [Month 9] Visit).
- Presence of a sustained positive inhibitor (≥0.6 BU/mL) after 48 weeks (12 months) of ITI treatment.
- Negative inhibitor titer without achieving either of the 2 PK parameters of ITI success after 48 weeks (12 months) of ITI treatment:
  - IR ≥1.32 IU/dL per IU/kg OR
  - $t_{½}$ ≥7 hours

Subjects who have been determined to have failed ITI will then proceed to the End of Treatment (EOT) Visit.

Partial success

Partial success is defined as achieving negative inhibitor titer and one of the PK parameters of ITI success: IR ≥1.32 IU/dL per IU/kg OR $t_{½}$ ≥7 hours.

The determination of partial success will be made only among subjects who have completed the maximum period of 48 weeks (12 months) of ITI treatment but do not fulfill the criteria for ITI success or treatment failure

Subjects who have been determined to have achieved only partial success will then proceed to EOT Visit.

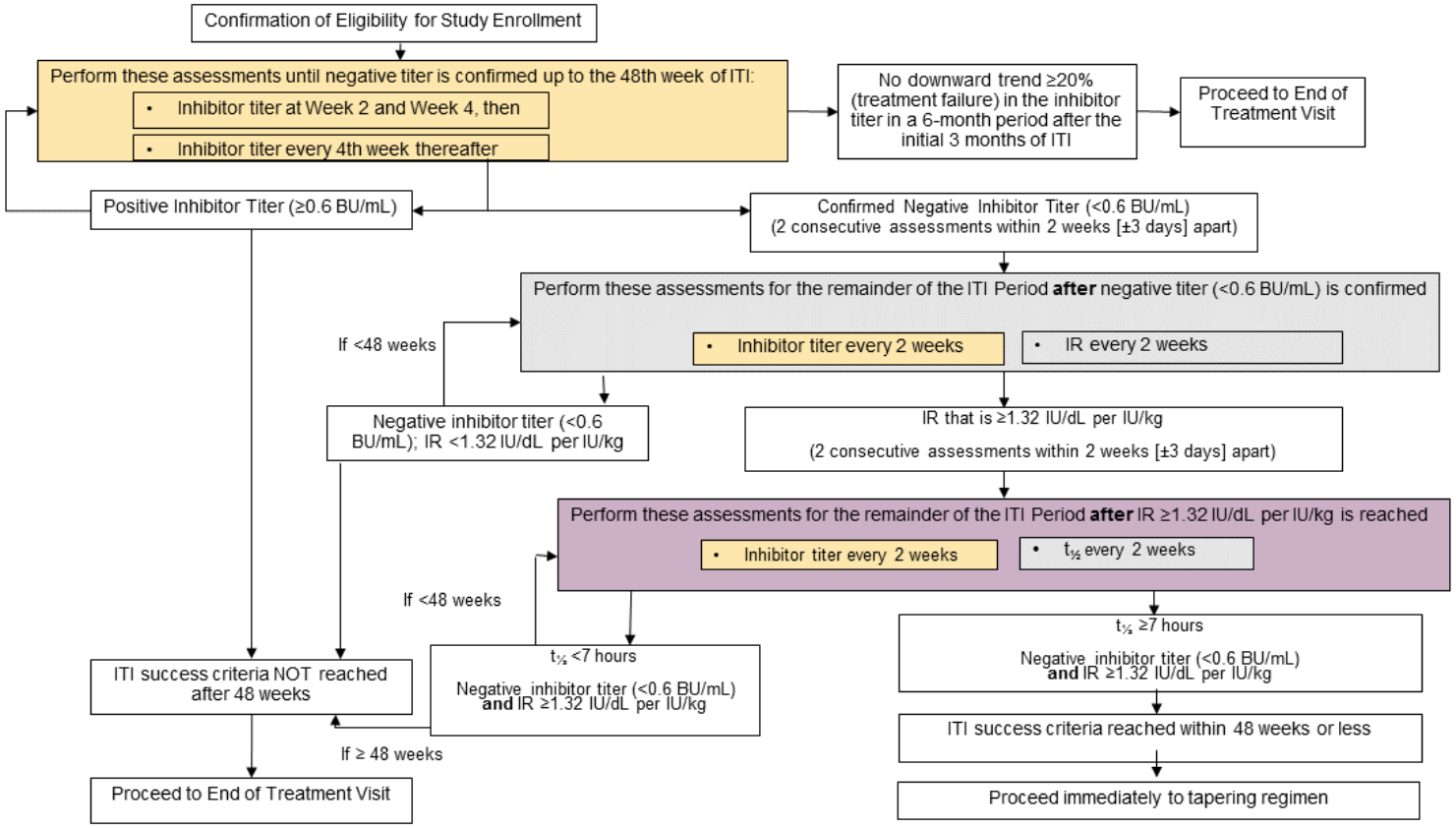
ITI success

ITI success is defined as achieving all 3 of the following criteria based on local laboratory results:

- Confirmed negative inhibitor titer (<0.6 BU/mL by the Nijmegen-modified Bethesda assay) based on 2 consecutive negative inhibitor assessments within 2 weeks (±3 days); determination of negative titer based on the Bethesda assay is acceptable at sites that have not yet adopted the Nijmegen-modified Bethesda assay

- IR ≥1.32 IU/dL per IU/kg, representing ≥66% of the expected IR 2 IU/dL per IU/kg (SmPC; USPI), at 2 consecutive assessments performed within 2 to 4 weeks
- $t_{½}$ ≥7 hours

Figure 2 Flow Diagram for Assessment of ITI Outcome



Abbreviations: BU=Bethesda unit; IR=incremental recovery; ITI=immune tolerance induction; $t_{½}$=half-life.
After confirmed negative inhibitor titer (<0.6 BU/mL), it is stated 'Perform these assessments (i.e. inhibitor titer every 2 weeks, and IR every 2 weeks) for the remainder of the ITI Period after negative titer (< 0.6 BU/mL) is confirmed'. Although this means that the sample for IR is drawn at the visit for the confirmatory negative inhibitor titer, however, the interpretation of the IR result will be performed after the negative inhibitor titer is confirmed.

7.2.3. Downtitration (Dose Adjustment) Between ITI Treatment and the Tapering Period

If FVIII activity levels rise above 200 IU/dL, after the inhibitors are negative but before all of the ITI success criteria are met, the dose will be adjusted according to Investigator judgment to maintain the FVIII activity levels between 100 and 200 IU/dL. This dose adjustment will not be considered part of the Tapering Period, and the subject will maintain the schedule of assessments per the ITI Period.

Once $t_{½}$ has been determined to be ≥7 hours, the Investigator may have a Tapering Initiation Visit and/or a Tapering Initiation Telephone Call. If the subject has already begun downtitration from the 200 IU/kg/day ITI dose, the subject will return for the next scheduled visit (the Tapering Initiation Visit) 2 weeks from the visit at which $t_{½}$ was determined to be ≥7 hours. If the subject has not already downtitrated when $t_{½}$ is determined to be ≥7 hours, the Investigator can make a telephone call to instruct the subject to begin downtitrating immediately (Tapering Initiation Telephone Call). Subject's subsequent visit, which will occur 2 weeks from the visit at which $t_{½}$ was determined to be ≥7 hours, will be the Tapering Initiation Visit.

7.2.4. Tapering Period

Subjects who have met the criteria for ITI success will enter the Tapering Period. Further details about the recommended dosing regimen for tapering are described in Section 11. Subjects with bleeding episodes during the Tapering Period will be tested for recurrence of inhibitors and monitored for relapse.

During the Tapering Period, treatment with bypassing agents may be considered if bleeding is unresponsive to treatment with rFVIIIFc (see Section 7.2.2.1). Testing for recurrence of inhibitors will be performed throughout the Tapering and Follow-Up Periods.

Subjects will visit the clinic 2 and 4 weeks after the first visit in the Tapering Period and then every fourth week for a minimum of 16 weeks (4 months). The duration of the Tapering Period may be modified by the Investigator with the Sponsor Medical Monitor's approval based on the subject's clinical response. If the Tapering Period exceeds 16 weeks (4 months), unscheduled visits will be performed every 4 weeks (1 month) or per the Investigator's judgment.

During the Tapering Period, subjects will undergo procedures and assessments at designated visits per the schedule of events (see Table 2). At each visit, samples for inhibitor titer and IR assessments will be drawn and sent to the local and central laboratories to monitor for relapse.

If the subject experiences bleeding during the Tapering Period, the treatment of the bleeding will be left to the discretion of the Investigator. During the Tapering Period, treatment with bypassing agents may be considered if bleeding is unresponsive to treatment with rFVIIIFc (see Section 7.2.2.1).

Throughout the Tapering Period, rFVIIIFc administration, bypassing agent administration, and any bleeding episodes will be collected by the subject and/or his caregiver in the EPD. The EPD data will be reviewed by the Investigator on an ongoing basis and discussed with the subject at each visit.

Relapse

If a subject experiences bleeding episodes that cannot be controlled with the use of rFVIIIFc, further investigation for relapse may be warranted.

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 (Hay & DiMichele, 2012):

- A positive inhibitor (≥0.6 BU/mL using the Nijmegen assay) on 2 consecutive assessments performed within 2 to 4 weeks; determination of positive titer based on the Bethesda assay is acceptable at sites that have not yet adopted the Nijmegen-modified Bethesda assay.

AND

- An IR <1.32 IU/dL per IU/kg (representing <66% of the expected IR) on 2 consecutive assessments performed within 2 to 4 weeks.

If any assessments indicate the possibility of relapse at any time during the Tapering or Follow-Up Period, the tests must be repeated at the following visit to confirm relapse. A subject with confirmed relapse (i.e., confirmation of both of the above criteria in 2 consecutive assessments) must complete the EOT Visit. At EOT, $t_{½}$ will be assessed and recorded.

7.2.5. Follow-Up

After completion of the Tapering Period, subjects will enter the Follow-Up Period, during which subjects will be treated prophylactically with the rFVIIIFc dose and interval prescribed by the Investigator, according to the label and clinical response of the subject, for 32 weeks (8 months). To avoid bleeding episodes and a relapse of the inhibitors, FVIII activity levels should be kept ≥1 IU/dL.

If the subject experiences a bleeding episode during the Follow-Up Period, the treatment of the bleed will be left to the discretion of the Investigator. Treatment with bypassing agents may be considered if bleeding is unresponsive to treatment with rFVIIIFc. Subjects with bleeding episodes during the Follow-Up Period will be tested for recurrence of inhibitors (see Section 7.2.2.1).

During the Follow-Up Period, the subject will visit the clinic every 12 weeks (3 months) and undergo procedures and assessments as per the schedule of activities (see Table 2). At each visit, samples for inhibitor titer and IR assessments will be drawn to monitor for relapse. A subject with confirmed relapse criteria will complete the EOT Visit as soon as possible.

7.2.6. End of Treatment/End of Study

At the EOT Visit, PK assessments to determine rFVIIIFc $t_{½}$ will be performed. $t_{½}$ determination at EOT Visit does not need to be performed if the full 4-sample $t_{½}$ assessment was performed within 2 weeks prior to the EOT Visit or if the Investigator determines the subject is an ITI Treatment Failure (see Section 7.2.2.2). Throughout the Follow-Up Period, rFVIIIFc

administration and any bleeding episodes will be collected by the subject and/or his caregiver in the EPD. The EPD data will be reviewed by the Investigator on an ongoing basis and discussed with the subject at each visit.

7.2.7. Final Safety Follow-Up

A Final Safety Follow-Up Visit or Follow-Up Telephone Call will take place within 7 to 14 days after the EOT Visit to monitor AEs, SAEs, and concomitant medications and procedures.

7.3. Unscheduled Visits

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

7.4. Study Stopping Rules

Sponsor may terminate this study at any time, after informing the Investigator(s). Sponsor will notify Investigator(s) if the study is placed on hold, completed, or terminated.

Sponsor may also stop the study for futility and not meeting the enrollment targets.

7.5. End of Study

The end of study is defined as last subject, last visit for final collection of data.

8. SELECTION OF SUBJECTS

8.1. Inclusion Criteria

To be eligible to participate in this study, candidates must meet the following eligibility criteria at the time of enrollment:

1. Ability of the subject or his legally authorized representative (e.g., parent or legal guardian) to understand the purpose and risks of the study and provide signed and dated informed consent and authorization to use protected health information in accordance with national and local subject privacy regulations
2. Male subjects of any age diagnosed with severe hemophilia A (as confirmed from the medical record)
3. Currently diagnosed with high-titer inhibitors (historical peak ≥5 BU/mL, according to medical records)
4. Previously treated with any pd-FVIII or recombinant conventional or Extended Half-Life FVIII
5. Canada specific requirements: See Appendix B.

8.2. Exclusion Criteria

Candidates will be excluded from study entry if any of the following exclusion criteria exist at the time of enrollment:

1. Other coagulation disorder(s) in addition to hemophilia A
2. Previous ITI
3. History of hypersensitivity or anaphylaxis associated with any FVIII administration
4. Planned major surgery scheduled during the study unless deferred until after study completion (minor surgery such as tooth extraction or insertion/replacement of central venous access device is allowed)
5. 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
6. Serum alanine aminotransferase or aspartate aminotransferase >5 × ULN as assessed by local laboratory
7. Serum total bilirubin >3 × ULN as assessed by local laboratory
8. Current enrollment or a plan to enroll in any interventional clinical study in which an investigational treatment or approved therapy, other than rFVIIIFc, for investigational use is administered within 30 days (or 5 half-lives of the agent, whichever is longer) prior to the Baseline Visit
9. Inability to comply with study requirements

10. Presence of any medical or psychological condition or laboratory result that, in the opinion of the Investigator, can interfere with the subject's ability to comply with the protocol requirements or make the subject not appropriate for inclusion to the study and treatment with Elocta®/Eloctate® (rFVIIIFc)
11. Other unspecified reasons that, in the opinion of the Investigator or Sponsor, make the subject unsuitable for enrollment
12. Unwillingness or inability to comply with the requirements of the protocol, including the presence of any condition (physical, mental, or social) that prevents the subject from participating in visits as scheduled or entering required information into the EPD in a timely manner
13. Concurrent systemic treatment with immunosuppressive drugs within 12 weeks (3 months) prior to Screening. Exceptions to this include ribavirin for treatment of hepatitis C virus (HCV), and/or systemic steroids (a total of 2 courses of pulse treatments lasting no more than 7 days within 12 weeks [3 months] prior to Day 1) and/or inhaled steroids
14. High risk of cardiovascular, cerebrovascular, or other thromboembolic events, as judged by the Investigator

The following criteria refer to tests performed within 26 weeks (6.5 months) prior to Screening. If not available, a new test will be drawn at the Screening Visit.

15. Cluster of differentiation 4 (CD4) lymphocytes <200 mm^3 at Screening, if known as human immunodeficiency virus (HIV) antibody positive based on medical history or HIV testing
16. Viral load of >400 copies/mL at Screening, if known as HIV antibody positive based on medical history

9. ENROLLMENT AND REGISTRATION, STUDY PROCEDURES

Once the investigational site has been activated for study participation, subjects may be enrolled if they have met the inclusion criteria in Section 8.1 and have not been excluded based on the exclusion criteria in Section 8.2.

9.1. Screening, Enrollment

Subjects or their legally authorized representative (e.g., parent or legal guardian), where applicable, must provide informed consent before any Screening tests or assessments are performed. Participating study sites are required to register all screened candidates in this study in the IXRS. If a subject is excluded from the study, the reasons for exclusion will be documented in the subject's documents.

9.2. Registration of Subjects

At the Screening Visit, IXRS will be used to assign each subject a unique 6-digit subject identification number (see Section 19.1.2). No subject may begin treatment prior to enrollment. Subject identification numbers that have been assigned will not be reassigned to another subject, even if the subject does not receive treatment. If a subject is rescreened, the subject may use his original number.

See the Study Reference Manual for details on registration.

10. DISCONTINUATION OF STUDY TREATMENT AND WITHDRAWAL OF SUBJECTS FROM THE STUDY

Subjects must be withdrawn from the treatment and the study for any one of the following reasons:

- The subject withdraws consent or the parent or legally authorized representative (e.g., parent or legal guardian) withdraws consent on behalf of the subject.
- The subject is unwilling or unable to comply with the protocol.
- The subject enrolls into another interventional clinical study in which an investigational treatment or approved therapy for investigational use is administered.
- ITI treatment is interrupted for >2 weeks.
- Emergent or elective surgery. Minor surgery such as tooth extraction or insertion/replacement of central venous access device is not a criterion for withdrawal.
- The subject received concomitant immunomodulation.
- The subject uses FVIII products other than rFVIIIFc (exception allowed for 1 emergency or accidental use).
- If, in the clinical judgment of the Investigator or Sponsor, it is not in the subject's best interest to continue with the study treatment.

The reason for the subject's withdrawal from the study must be recorded in the subject's electronic case report form (eCRF). When a subject is withdrawn, the date of study treatment dose and the date and reason for treatment/study withdrawal (see above) will be clearly described in the relevant sections of the eCRF. If a subject is removed from treatment because of an AE, the reason for treatment withdrawal will be stated as "adverse event" irrespective of whether this was the Investigator's or the subject's decision. This subject will be followed until the event has resolved, stabilized, or returned to baseline.

The withdrawn subject will be examined as soon as possible, whenever possible, irrespective of the reason for withdrawal. Subjects who are withdrawn will not be replaced. Relevant samples will be obtained, and all relevant assessments will be completed, preferably according to the schedule for EOT Visit. The eCRF will be completed as much as possible.

11. STUDY TREATMENT

The Sponsor will provide rFVIIIFc to sites in all countries.

11.1. Dosing Regimen and Administration

Refer to and follow the package insert or the Directions for Handling and Administration (DHA). See Section 5.4 for the rationale for the selected dosage regimen, dose levels, and treatment duration.

During the ITI Period, the rFVIIIFc dose administered is 200 IU/kg/day (±8 hours), which may be given as a once-daily dose or divided into several doses per day. If FVIII activity levels rise above 200 IU/dL, after the inhibitors are negative but before all of the ITI success criteria are met, the dose will be adjusted according to Investigator judgment to maintain the FVIII activity levels between 100 and 200 IU/dL (see Table 4).

During the Tapering Period (with all 3 tolerization success criteria met), the rFVIIIFc dose administered will be adjusted according to Investigator judgment based on the FVIII activity levels to maintain the FVIII activity levels between 100 and 200 IU/dL during the initial part of the Tapering Period, with the aim of tapering the rFVIIIFc dose to reach a prophylactic dosing regimen within 16 weeks (4 months).

An example of a dose adjustment schedule after the inhibitor titer has become negative and the subject has not met all the criteria for a successful tolerization is shown in Table 4. The dose adjustment will be individualized according to each subject's FVIII activity levels during this period.

Table 4 Example of a Dose Adjustment Schedule: Negative Inhibitor, Not All Success Criteria Met

Peak FVIII Activity Levels	Dose of rFVIIIFc per Day
<200 IU/dL	200 IU/kg/day
≥200 IU/dL	100 IU/kg/day

Abbreviations: FVIII=coagulation factor VIII; rFVIIIFc=recombinant coagulation factor VIII Fc fusion protein.

During the Tapering Period (with all 3 tolerization success criteria met), the aim is to keep FVIII activity levels approximately between 100 and 200 IU/dL for at least 4 weeks (1 month), with the aim of tapering the dose to reach the prophylactic dosing regimen within at least 12 weeks (3 months) (see Table 5). It is recommended that the entire Tapering Period be at least 16 weeks (4 months). This schedule is only an example, and each subject's tapering schedule is left to the treating physician's discretion.

Table 5 Example of a Dose Tapering Schedule: All 3 Success Criteria Met

Tapering Period	Dose and Interval
Weeks 1 to 6	100 IU/kg QD
Weeks 6 to 12	100 IU/kg QOD
Weeks 12 to 16	50 IU/kg QOD
Week 16 onward	50 IU/kg 3 times per week (prophylaxis)

Abbreviations: QD=once a day; QOD=every other day.

During the Follow-Up Period, the prophylaxis regimen will be adjusted based on clinical response and with the goal of keeping FVIII activity levels ≥1 IU/dL at all time points according to Investigator judgment and local practice.

If the subject misses a dose, the Investigator should be notified, and the Investigator will determine when the next dose of rFVIIIFc should be taken.

Bleeding episodes occurring during the study will be treated per Investigator judgment and within labeled dosing recommendations. Concomitant treatment with bypassing agents such as aPCC (FEIBA) or rFVIIa (NovoSeven) will be allowed during the ITI Period under certain circumstances (see Section 7.2.2.1 for details).

11.1.1. 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 intravenous (IV) injection over several minutes, at a rate of administration determined by the subject's comfort level.

Because of the risk of allergic reactions with FVIII concentrates, the initial administration of rFVIIIFc will be performed under medical observation, where proper medical care for allergic reactions could be provided. Subjects/caregivers will be instructed to administer subsequent rFVIIIFc doses at home, except for the dose given prior to assessments of rFVIIIFc $t_{½}$ and IR, which will be administered in the clinic.

It is recommended that the subject/caregiver enter dosing information on rFVIIIFc and/or FVIII bypassing agents into the EPD immediately after an injection or within a maximum of 7 days, to ensure data integrity and to facilitate appropriate medical review and dosing guidance. Complete instructions for the preparation and administration of rFVIIIFc are provided in the DHA within the Study Reference Manual.

11.1.2. Calculation and Recording of Dosing Based on Actual Potency and Dosing Based on Nominal Strength

Actual potency dosing is required for the dose of 50 IU/kg used to measure IR and $t_{½}$ during the study. The actual potency shown on the vial must be used to calculate the units of rFVIIIFc and the volume to inject.

Note: The instructions and worksheets provided in the DHA must be used to calculate the volume for administration based on actual potency. The actual potency shown on the vial must be used to calculate the volume for administration.

The nominal strength is defined as the target potency of the vial (i.e., 250, 500, 1000, 2000, or 3000 IU per vial). Nominal strength will be used for all other rFVIIIFc dose calculations, and whole vials will be used to achieve the target dose, rounded to the nearest 250 IU.

11.1.3. Prior and Concomitant Therapy

A concomitant therapy is any drug or substance administered from 30 days prior to the Screening Visit through the Final Safety Follow-Up Visit. Bypassing agents used during the study are considered concomitant therapy and should be recorded as such. For subjects 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 subjects or caregivers will be instructed that the subject should not start any new medications, including nonprescription drugs and herbal preparations, unless they have received permission from the Investigator.

11.1.4. Allowed Concomitant Therapy

Therapy considered necessary for the subject's welfare, including routine immunizations, may be given at the discretion of the Investigator. Bypassing agents (e.g., aPCC [FEIBA] or rFVIIa [NovoSeven]) are allowed in subjects as outlined in Section 7.2.2.1. All such therapy must be recorded in the eCRF. The prophylactic use of bypassing agents in subjects requires discussion with the Sponsor Medical Monitor and documentation of rationale.

11.2. Compliance

Compliance with treatment dosing is to be monitored and recorded by site staff.

The date and time of the rFVIIIFc administrations on Day 1 and the doses given prior to assessments of rFVIIIFc $t_{½}$ and IR, which will be administered in the clinic, will be recorded in the eCRF. The date, time, amount of, and reason for rFVIIIFc administrations done outside the clinic will be recorded by the subject/caregiver in the EPD. The EPD data will be reviewed on an ongoing basis by study site staff and the Clinical Monitor.

11.3. Excluded Concomitant Therapies and Procedures

A concomitant procedure is any therapeutic intervention (e.g., surgery/biopsy, 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 reason for all concomitant procedures performed during the study will be documented in the medical records and recorded in the eCRF. AEs related to administration of these procedures must be documented on the appropriate eCRF.

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

The following concomitant medications are not permitted during the study:

- 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.
- Emicizumab® (Hemlibra)
- Any other FVIII

During the Tapering Period, treatment with bypassing agents may be considered if bleeding is unresponsive to treatment with rFVIIIFc (see Section 7.2.3). It is recommended that subjects be tested for inhibitors. See Section 7.2.2.1 for additional details regarding use of bypassing agents.

Subjects will be instructed to contact their Investigators before taking any new medications, including nonprescription drugs and herbal preparations.

12. STUDY TREATMENT MANAGEMENT

12.1. rFVIIIFc Stability and Storage

rFVIIIFc is supplied in kits comprising a single-use vial containing nominally 250, 500, 1000, 2000, or 3000 IU of factor VIII potency, a pre-filled syringe with 3 mL of sterile water for injection, and a sterile vial adapter (reconstitution device). The actual amount of rFVIIIFc in IU is stated on the label and carton of each vial. Any of the potencies listed may be used. The label will include conditions for storage, lot number, and other pertinent information such as Sponsor and caution statement.

Study treatment must be stored in a secure location. Accountability for study treatment is the responsibility of the Investigator. More details concerning this responsibility are included in Section 12.2.

Study treatment must only be dispensed by a Pharmacist or a medically qualified staff. Study treatment is to be dispensed only to a subject (or subject's legally authorized representative) enrolled in this study. Once study treatment is prepared for a subject, it can only be administered to that subject. Study treatment vials are for 1-time use only; any study treatment remaining in the vial cannot be used for another subject.

Study site staff will refer to the approved package insert and DHA for specific instructions on the handling, preparation, administration, and disposal of the study treatment.

12.1.1. rFVIIIFc Preparation

The individual preparing rFVIIIFc will first carefully review the instructions provided in the approved package insert and the DHA.

If the packaging is damaged, or if there is anything unusual about the appearance or attributes of the vials or drug, it cannot be used. The vial in question will be saved at the study site, and the problem will be immediately reported to Sponsor.

12.1.2. rFVIIIFc Handling and Disposal

The Investigator must return all used and unused kits of rFVIIIFc as instructed by Sponsor unless approved for onsite destruction. The instructions for returning the kits will be provided at the time the request is made by Sponsor.

If any Sponsor supplies are to be destroyed at the study site, the institution or appropriate site personnel must obtain prior approval from Sponsor by providing, in writing, the destruction policy or details of the method of destruction. After such destruction, the institution/Principal Investigator(s) must notify Sponsor, in writing, of the details of the study treatment destroyed (e.g., lot or kit numbers, quantities), the date of destruction, and proof of destruction.

12.2. rFVIIIFc Accountability

Accountability for study treatment is the responsibility of the Investigator. The study site must maintain accurate records demonstrating the date and amount of study treatment received, to whom dispensed (subject-by-subject accounting), amount returned by the subject, and accounts of any study treatment accidentally or deliberately destroyed. These records will be routinely reviewed by the Clinical Monitor during the monitoring visits.

Unless otherwise notified, the subject's parents/legal guardians must return all vials (used and unused) at each clinic visit for full medication exchange and accountability. At the end of the study, reconciliation must be made between the amount of drug product supplied, dispensed, and subsequently destroyed, lost, or returned to Sponsor. A written explanation must be provided to Sponsor for any discrepancies.

13. EFFICACY AND PHARMACOKINETIC ASSESSMENTS

Laboratory samples will be drawn for assessment of inhibitor titer (Nijmegen-modified Bethesda assay) and FVIII activity (1-stage activated partial thromboplastin time [aPTT] assay) and analyzed. These samples will be analyzed at the local laboratory and at a central laboratory. The Investigators will use local laboratory results for purposes of decision-making. Bethesda assay results are acceptable at sites that have not yet adopted the Nijmegen-modified Bethesda assay. Laboratory samples will be obtained for local assessment of hematology, blood chemistry, and urinalysis. Administration of rFVIIIFc, administration of bypassing agents, occurrence of bleeding episodes (spontaneous and traumatic), and associated details will be collected through the EPD. If blood volume sufficient for all samples cannot be drawn, please refer to the Study Reference Manual for a list of prioritization of samples.

See Section 4.2 for the timing of all assessments.

13.1. Clinical Efficacy Assessments

If there is a limitation on blood draw volume, the local laboratory sample will be prioritized. If the local laboratory results cannot be interpreted, the Investigator may use the central laboratory results.

Analysis of ITI outcome will be based on the Investigator's assessment of local laboratory data and will be entered into the eCRF. If the local laboratory results cannot be interpreted, the Investigator may use the central laboratory results to assess ITI outcome.

13.1.1. Assessment of Inhibitor Titers

Sampling procedure and bioanalytical method

Blood samples for the determination of FVIII inhibitors will be collected at all visits during the study. The procedures for blood collection, processing into plasma, storing, and transporting to the central laboratory are fully described in the laboratory section of the Study Reference Manual. Samples for inhibitor testing and assessment of FVIII activity levels will be analyzed at the local laboratory and at a central laboratory.

Subjects have fulfilled the first criteria for ITI success after confirmation of negative titers consisting of 2 consecutive negative inhibitor assessments within 2 weeks (±3 days) based on local laboratory results <0.6 BU/mL by the Nijmegen-modified Bethesda assay; determination of negative titer based on the Bethesda assay is acceptable at sites that have not yet adopted the Nijmegen-modified Bethesda assay.

13.1.2. Assessment of Incremental Recovery

13.1.2.1. FVIII Activity

A blood sample will be collected for monitoring of FVIII activity at each visit where IR or $t_{½}$ is not assessed, starting from Week 2.

Sampling for incremental recovery

Blood samples will be collected for analysis of rFVIIIFc activity for assessment of IR starting at the visit **for** confirmed negative titers and at all consecutive visits, except for those visits at which samples for rFVIIIFc $t_{½}$ determination are drawn, as IR will be determined from the same samples. Samples for IR will be analyzed at the investigational site's local laboratory and confirmed at the central laboratory, with results being entered into the eCRF. Testing for IR will continue, until 2 consecutive assessments represent ≥66% of the expected IR (≥1.32 IU/dL per IU/kg).

Subjects must not be currently bleeding and are required to have at least a 24-hour washout prior to the IR predose sample collection. The sample for IR will be drawn within 30 minutes prior to and 30 (±5) minutes after a 50 IU/kg rFVIIIFc injection administered via a slow push IV injection over several minutes, at a rate of administration determined by the subject's comfort level. Volume and units of factor infused must be calculated and recorded using the actual potency as described in the DHA included in the Study Reference Manual.

According to the local standard of care, an IV access device may be offered to facilitate sample collection. Whenever possible, sites are instructed to avoid the use of heparin when drawing PK samples. When this is not possible, sites must follow local protocols to ensure heparin is adequately removed prior to the PK sample collection. The IV access device must not be flushed with heparin between injection of rFVIIIFc and the collection of the samples.

Once the sample for IR has been collected, the subjects can be given the remainder of their daily ITI dose.

The procedures for blood collection, processing into plasma, storing, and transporting to the central laboratory are fully described in the laboratory section of the Study Reference Manual. The plasma samples will be analyzed for FVIII activity at the study's central laboratory using a validated 1-stage clotting assay.

Subjects have fulfilled the second criterion for ITI success after achieving rFVIIIFc IR ≥1.32 IU/dL per IU/kg on 2 consecutive assessments performed within 2 weeks (±3 days) (see Section 7.2.2.2).

13.1.2.2. Calculations

The IR will be calculated as the difference between the FVIII activity level at 30 ± 5 minutes postdose (C_{30min}) and the FVIII predose activity level ($C_{predose}$) divided by the dose, i.e., $IR = (C_{30min} - C_{predose}) / Dose$. Factor VIII activity levels below the lower limit of quantitation will be treated as zero. The actual dose of rFVIIIFc will be used to calculate the IR and $t_{½}$.

Calculations of IR will be done by the Investigator or designee according to the instructions in the DHA included in the Study Reference Manual.

13.1.3. Assessment of rFVIIIFc Half-Life

13.1.3.1. Sampling for rFVIIIFc t½

Blood samples will be collected for local and central laboratory analyses of rFVIIIFc activity for assessment of rFVIIIFc t½ at the visit after rFVIIIFc IR ≥1.32 IU/dL per IU/kg has been confirmed at 2 consecutive assessments performed within 2 weeks (±3 days). The assessment will be repeated at each consecutive visit until rFVIIIFc t½ is ≥7 hours and also at the EOT Visit. If t½ is <7 hours, subjects need to return to clinic in 2 weeks (±3 days) to complete another t½ assessment until ITI success or 48 weeks (12 months). t½ determination at EOT Visit does not need to be performed if the complete 4-sample t½ assessment was performed within 2 weeks prior to the EOT Visit or if the Investigator determines the subject is an ITI Treatment Failure (see Section 7.2.2.2).

PK assessment of t½ requires sampling at multiple timepoints. During the ITI Period, the Investigator may forego the fourth PK sample, i.e., the 30- or 48-hour sample, if, in the Investigator's opinion, the t½ at the third PK sample indicates that a t½ ≥7 hours cannot be achieved. In this case, the Investigator will document the decision to forego the fourth sample.

Samples will be drawn according to the times indicated in Table 3. According to the local standard of care, an IV access device may be offered to facilitate sample collection. Whenever possible, sites are instructed to avoid the use of heparin when drawing PK samples. When this is not possible, sites must follow local protocols to ensure heparin is adequately removed prior to the PK sample collection. The IV access device must not be flushed with heparin between injection of rFVIIIFc and the collection of the samples.

Additionally, a saline lock of the infusaport can be used for the 30-minute and 6-hour post-dose samples instead of heparin. Heparin may then be used for overnight maintenance of the infusaport for the remainder of the samples. Standard technique for clearing the infusaport of heparin should be employed prior to the 24- and 30-/48-hour post-dose samples. Sites are advised to refer to their local standard of care regarding maintenance of the IV access device.

Subjects must not be currently bleeding and are required to have at least a 24-hour washout prior to the rFVIIIFc t½ predose sample collection. A dose of 50 IU/kg of rFVIIIFc for assessments will be delivered via a slow push IV injection over several minutes, at a rate of administration determined by the subject's comfort level. Volume and units of factor infused must be calculated and recorded using the actual potency as described in the DHA included in the Study Reference Manual. Subjects will not have any additional doses of rFVIIIFc during the PK Sampling Period. If emergency dosing is required during the t½ Sampling Period, inform the Sponsor and the t½ assessment will be rescheduled.

Once the final sample for t½ has been collected, the subjects can be given their daily ITI dose.

Subjects have fulfilled the third and last criterion for ITI success after a FVIII activity t½ ≥7 hours has been determined by the local and/or central laboratories (see Section 7.2.2.2).

During the Tapering and Follow-Up Period, if a subject meets the criteria for relapse, he will then proceed to the EOT Visit, at which t½ will be assessed.

13.1.3.2. Calculations

Calculations of $t_{½}$ will be done by the Investigator/designee and Sponsor. Calculations will be performed according to the instructions in the DHA included in the Study Reference Manual.

13.1.4. Assessment of Bleeding Episodes

13.1.4.1. Definition of a Bleeding Episode

A bleeding episode starts from the first sign of a bleed and ends no more than 72 hours after the last injection of bypass agents or rFVIIIFc to treat the bleeding episode, within which any symptoms of bleeding at the same location, injections less than or equal to 72 hours apart, are considered the same bleeding episode. Any injection of bypass agents (or rFVIIIFc during tapering or follow-up) 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.

Type of bleeding episode

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

Spontaneous bleeding episodes

Bleeding episodes will be classified as spontaneous if a subject or caregiver records a bleeding event if there is no known contributing factor such as a definite trauma or antecedent “strenuous” activity. The determination of “strenuous” is at the discretion of the Investigator, and the parent/caregiver/subject needs to be instructed by the Investigator.

Traumatic bleeding episodes

Bleeding episodes will be classified as traumatic if the subject or caregiver records a bleeding episode even when there is a known or believed reason for the bleed. For example, if a subject exercises strenuously and then has 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 will consider whether events resulting in a traumatic bleeding episode qualify as AEs and should be reported as such.

Reporting of bleeding episodes

Bleeding episodes in this patient population are not considered as AEs. However, the concomitant events associated with a bleeding episode will be reported as AEs as appropriate (e.g., an elbow fracture). Bleeding episodes that meet a criterion for seriousness will be reported as an SAE. All bleeding episodes will be captured in the EPD that the subject maintains throughout the study.

13.1.4.2. Data to Be Captured

It is required that the subject/caregiver enter dosing information on rFVIIIFc and/or FVIII bypassing agents into the EPD immediately after an injection or within a maximum of 7 days, to ensure data integrity and to facilitate appropriate medical review and dosing guidance.

In the event of a bleeding episode, the following information will be collected in the EPD or eCRF and medical records:

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

The EPD will serve as the source document for bleeding episodes between visits. Bleeding episodes during clinical visits will be recorded in the eCRF.

The clinical sites and Clinical Monitors will ensure that there is consistency between the subject's medical record, dispensing records, source documents, EPD, and eCRFs. During the clinic visits, the Investigator will verify whether a bleeding episode has occurred and was "spontaneous" or "traumatic." The subject or caregiver will also be reminded about timely EPD completion.

13.2. Medical History Assessments

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

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 (if positive, viral load, CD4 count, and platelets; based on laboratory results within the last 26 weeks [6.5 months]), hepatitis B virus, HCV, medication history, and any other congenital immunodeficiency.

Hemophilia history includes (but is not limited to) the date of diagnosis; severity of disease, family history of hemophilia, and genotype; blood group; number of prior exposures to FVIII; last dose regimen; and type of FVIII (recombinant, plasma derived with von Willebrand factor (VWF) or plasma derived without VWF prior to inhibitor development.

Inhibitor history includes peak historical inhibitor titer, age at the time of inhibitor detection, and exposure days at inhibitor development.

Bleeding episode history in the 12 months (48 weeks) prior to Baseline includes date, location, type of bleeding episode (e.g., spontaneous or traumatic), and treatment of the bleeding episode.

13.3. Demography

Demographic data to be collected will include, but will not be limited to, the subject's age at Screening, sex, race and ethnicity (unless not able to be reported due to local regulations), body weight, body length, and geographic location and will be recorded in the eCRF at the Screening Visit. The body weight recording will be repeated at each visit as specified in the Schedules of Activities (see Section 4.2). Height will also be recorded at Screening and EOT Visit.

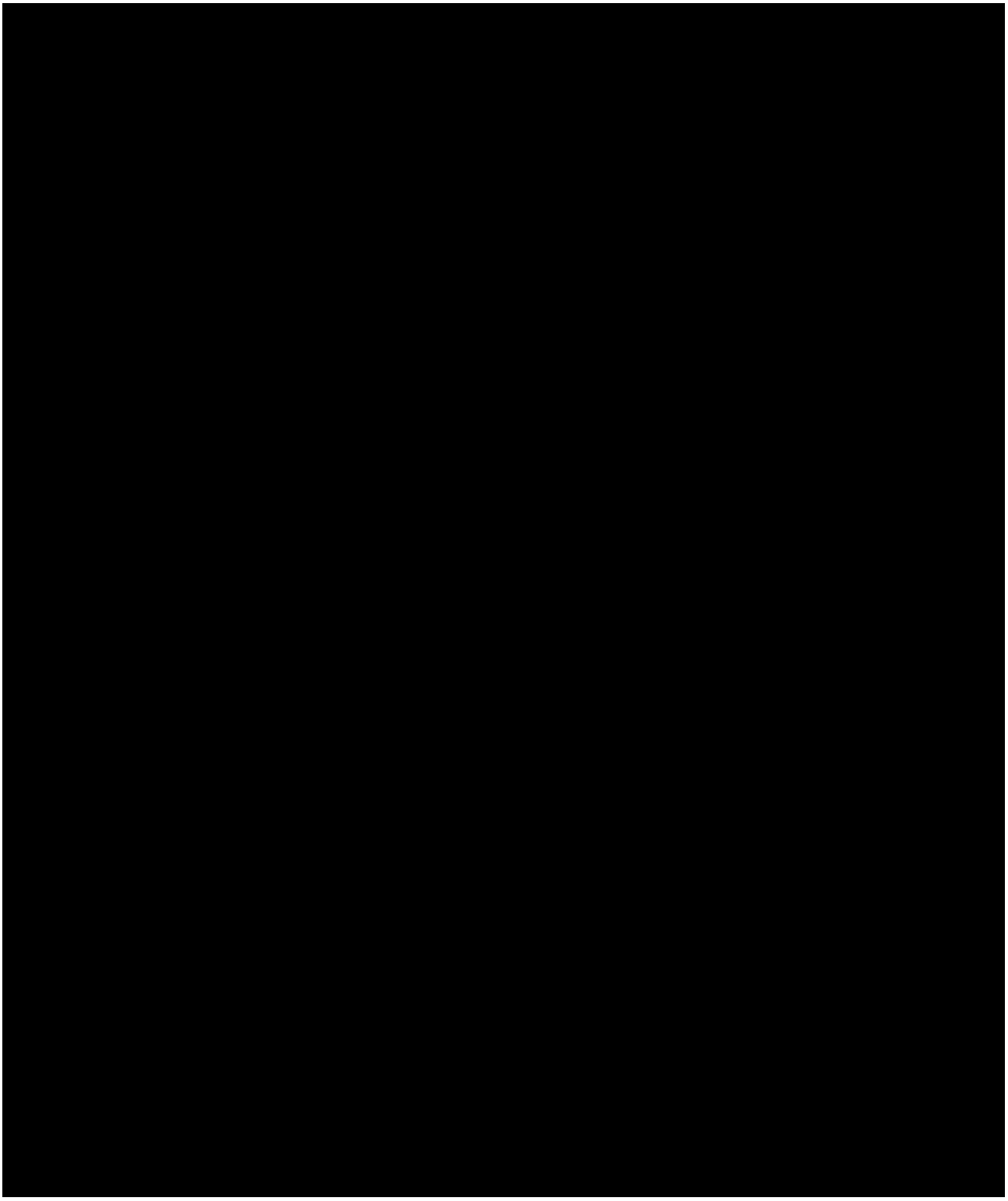
13.4. Pharmacoeconomic Assessments

Consumption will be assessed based on the amount of administered study treatment as recorded in the eCRF and in the EPD.

The date and time of the in-clinic administrations of rFVIIIFc will be recorded in the eCRF by the Investigator or designee. The date, time, amount of, and reason for any study treatment administrations done outside the clinic will be recorded by the subject/caregiver in the EPD.

Subject's days missed from school or work will be recorded in the EPD. Hospitalizations will be captured as SAEs.

13.5. Exploratory Laboratory Assessments



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14. SAFETY ASSESSMENTS

See Section 4.2 for the timing of all safety assessments.

14.1. Clinical Safety Assessments

The following clinical assessments will be performed to evaluate the safety profile of rFVIIIFc:

- Physical examinations
- Vital sign measurements (body temperature, blood pressure, pulse rate, and respiratory rate) should be taken prior to and 20 (±5) minutes after the end of the rFVIIIFc injection (if dosing occurs at the visit)
- Weight and height measurements
- Concomitant therapy and procedure recording
- AE and SAE recording

14.2. Laboratory Safety Assessments

Blood samples for determination of hematology and blood chemistry variables and urine dipstick will be collected at Screening Visit, Baseline Visit (before the first study treatment administration), and then every 12 weeks (3 months) from the start of the ITI Period through the time of ITI complete success. These assessments will be collected every 12 weeks (3 months) during the Tapering Period. If the subject completes the ITI Period in a duration shorter than 12 weeks (3 months), these assessments must be completed at the end of the period. Samples will also be collected at the EOT Visit. The date of blood and urine collection will be recorded in the eCRF.

The following laboratory tests will be performed at a local laboratory to assess the safety profile of rFVIIIFc:

- 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.
- Dipstick urinalysis, including a protein reading; if the protein reading is positive (≥1+), a full laboratory urinalysis will be performed.

Clinically significant abnormal laboratory values should be reported as AEs at the discretion of the Investigator. The corresponding result should be entered into the eCRF together with information on laboratory variable assessed, date of sample, and normal range from the local laboratory.

For Canada specific requirements:see Appendix B.

The volume of blood taken from the subjects: the study-related blood loss should not exceed 3% of the total blood volume during a period of 4 weeks (1 month) and should not exceed 1% of the total blood volume at any single time (see Table 6 and Section 14.5).

14.3. Vital Signs

Vital signs (blood pressure [systolic and diastolic], pulse rate, respiratory rate, and body temperature) will be assessed at each visit. Vital signs should be taken prior to and 20 (±5) minutes after the end of the rFVIIIFc injection (if dosing occurs at the visit).

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

Abnormal vital sign values that the Investigator determines are clinically significant should be reported as AEs (see Section 15.1 for details).

14.4. Physical Examination

A general physical examination will be assessed and recorded as "normal" or "abnormal" at each visit. Abnormalities will be specified. Any persisting abnormalities will be stated each time the examination is performed. Diagnosis of new abnormalities will be recorded as AEs. If any abnormalities are reported at the Screening Visit, they will be recorded as medical history.

14.5. Sample Volumes

The volume of blood taken from the subjects should comply with the European Commission guidance (European Commission, 2008) for recommended blood draw volume limits for pediatric patients, that is, the study-related blood loss should not exceed 3% of the total blood volume during a period of 4 weeks (1 month) and should not exceed 1% of the total blood volume at any single time. Examples of recommended blood draw volume limits per the European Commission guidance are provided in Table 6. Local and/or regional guidelines regarding blood draw volumes may also apply.

Subjects of low body weight may require Screening blood draws over multiple days to comply with maximum allowable blood draw volumes (see Table 6). Alternatively, individual Investigators may choose to collect all Screening samples using a single blood draw, after weighing the risk associated with multiple venipuncture attempts versus that of drawing all required samples at a single time. If the option of a single blood draw is chosen, the Investigator must document the rationale.

The laboratory section of the Study Reference Manual will define which laboratory assessments to prioritize to ensure that the maximum allowed blood volume is not exceeded.

Table 6 Examples of Recommended Blood Draw Volume Limits

Subject Weight (kg)	Blood Draw Limits (mL)[1]	
	Single Occasion	4 Weeks[2]
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
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

[1] Based on an estimated blood volume of 80 mL/kg.
[2] Based on the European Commission guidance (European Commission, 2008) for recommended blood draw volume limits for pediatric patients, recommending that blood draw volumes not exceed 1% of the total blood volume on a single occasion or 3% of the total blood volume over a 4-week (1-month) period.

15. SAFETY DEFINITIONS, RECORDING, REPORTING, AND RESPONSIBILITIES

Throughout the course of the study, every effort must be made to remain alert to possible AEs. If an AE occurs, the first concern should be for the safety of the subject. If necessary, appropriate medical intervention should be provided.

At the signing of the ICF, each subject or his legally authorized representative and/or main caregiver must be given the names and telephone numbers of study site staff for reporting AEs and medical emergencies.

SAEs will be collected from the time of signing ICF to the Final Safety Follow-Up Visit/Telephone Call. AEs will be collected from the time of the first dose of rFVIIIFc to the Final Safety Follow-Up Visit/Telephone Call.

See Section 4.2 for the timing of all assessments.

15.1. Definitions

15.1.1. Adverse Event

An AE is any untoward medical occurrence in a subject or clinical investigation subject administered a pharmaceutical product that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

Bleeding episodes in this subject population are not considered AEs. Bleeding episodes that meet a serious criterion must be reported as an SAE. All bleeding episodes that occur outside the clinic or hospital will be captured in the EPD that the subject or the subject's caregivers will be maintaining throughout the study period. EPD data must be entered within 7 days.

Determination of whether an abnormal laboratory value meets the definition of an AE will be made by the Investigator. Although abnormal laboratory values are typically not considered AEs, the following considerations may result in an abnormal laboratory value being considered an AE:

- A laboratory test result that meets the criteria for an SAE
- A laboratory test result that requires the subject to receive specific corrective therapy
- A laboratory abnormality that the Investigator considers to be clinically significant

Preexisting Conditions

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

Procedures

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

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."

15.1.2. Serious Adverse Event

An SAE is any untoward medical occurrence that at any dose:

- Results in death
- In the view of the Investigator, places the subject at immediate risk of death (a life-threatening event); however, this does not include an event that, had it occurred in a more severe form, might have caused death
- Requires subject hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Results in a congenital anomaly/birth defect

An SAE may also be any other medically important event that, in the opinion of the Investigator, may jeopardize the subject or may require intervention to prevent 1 of the other outcomes listed in the definition above. (Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or convulsions occurring at home that do not require subject hospitalization.).

15.2. Safety Classifications

15.2.1. Investigator Assessment of Events

All events must be assessed to determine the following:

- If the event meets the criteria of an SAE as defined in Section 15.1.2
- The relationship of the event to study treatment as defined in Section 15.2.2
- The severity of the event as defined in Section 15.2.3.

15.2.2. Relationship of Events to Study Treatment

The following definitions should be considered when evaluating the relationship of AEs and SAEs to the study treatment:

Relationship of Event to Commercial Drug	
Not related	An AE is considered "not related" to the use of the investigational drug if there is not a possibility that the event has been caused by the product under investigation. Factors pointing toward this assessment include, but are not limited to: the lack of reasonable temporal relationship between administration of the drug and the event, the presence of a biologically implausible relationship between the product and the AE (e.g., the event occurred before administration of drug), or the presence of a more likely alternative explanation for the AE.
Related	An AE is considered "related" to the use of the investigational drug if there is a possibility that the event may have been caused by the product under investigation. Factors that point toward this assessment include, but are not limited to: a positive re-challenge, a reasonable temporal sequence between administration of the drug and the event, a known response pattern of the suspected drug, improvement following discontinuation or dose reduction, a biologically plausible relationship between the drug and the AE, or a lack of an alternative explanation for the AE.

Abbreviation: AE=adverse event.

15.2.3. Severity of Events

The following definitions should be considered when evaluating the severity of AEs and SAEs:

Severity of Event	
Mild	Symptom(s) barely noticeable to subject or does not make subject uncomfortable; does not influence performance or functioning; prescription drug not ordinarily needed for relief of symptom(s) but may be given because of personality of subject.
Moderate	Symptom(s) of a sufficient severity to make subject uncomfortable; performance of daily activity is influenced; subject is able to continue in study; treatment for symptom(s) may be needed.
Severe	Symptom(s) cause severe discomfort; symptom(s) cause incapacitation or significant impact on subject's daily life; severity may cause cessation of treatment with study treatment; treatment for symptom(s) may be given and/or subject hospitalized.

15.2.4. Expectedness of Events

Expectedness of all AEs will be determined by Sponsor Pharmacovigilance according to the Investigator Brochure.

15.3. Monitoring and Recording Events

15.3.1. Adverse Events

Any AE experienced by the subject between the time of the first dose of study treatment and the Safety Follow-Up Visit/Telephone Call is to be recorded on the subject's eCRF, regardless of the severity of the event or its relationship to study treatment.

15.3.2. Serious Adverse Events

Any SAE experienced by a subject between the time of signature of the ICF and the Safety Follow-Up Visit/Telephone Call is to be recorded on an SAE Form, regardless of the severity of the event or its relationship to study treatment. SAEs must be reported to IQVIA Pharmacovigilance and the designated personnel within 24 hours, as described in Section 15.3.3 . Follow-up information regarding an SAE also must be reported within 24 hours.

Bleeding episodes in this patient population are not considered as AEs. However, the concomitant events associated with a bleeding episode will be reported as AEs as appropriate (e.g., an elbow fracture). Bleeding episodes that meet a criterion for seriousness will be reported as an SAE. All bleeding episodes will also be captured in the EPD that the subject maintains throughout the study.

Any SAE ongoing when the subject completes the study or discontinues from the study will be followed by the Investigator until the event has resolved, stabilized, or returned to Baseline status.

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/mL) after ITI success, during the Tapering and Follow-Up Periods (i.e., relapse of an inhibitor)
- A subject 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 World Health Organization scale (WHO, 1979):
  - Grade 2: bronchospasm; no parenteral therapy needed
  - Grade 3: bronchospasm; parenteral therapy required
  - Grade 4: anaphylaxis
- A subject develops a vascular thrombotic event, with the exception of IV injection site thrombophlebitis

Allergic reactions, including anaphylaxis, have been reported with FVIII products. The subjects/caregivers must 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 subjects/caregivers must be instructed to seek immediate medical care.

The subject and/or the subject'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, 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 subject is at home, the subject and/or the subject's caregivers will be instructed to seek immediate medical care for the subject.

15.3.3. Immediate Reporting of Serious Adverse Events

To adhere to all applicable laws and regulations for reporting an SAE, the study site must formally notify IQVIA Pharmacovigilance within 24 hours of the study site staff becoming aware of the SAE. It is the Investigator's responsibility to ensure that the SAE reporting information and procedures are used and followed appropriately.

Reporting Information for SAEs

Any SAE that occurs between the time that the subject or subject's parents/legal guardian has signed the ICF and 7 to 14 days after the EOT Visit (Final Safety Follow-Up Visit/Telephone Call) must be reported to IQVIA Pharmacovigilance within 24 hours of the study site staff becoming aware of the event.

A report must be submitted regardless of the following:

- **Whether or not the subject has undergone study-related procedures**
- **Whether or not subject has received study treatment**
- **The severity of the event**
- **The relationship of the event to study treatment**

To report initial or follow-up information on an SAE, fax a completed SAE form to IQVIA Pharmacovigilance at the country-specific fax numbers provided in the Study Reference Manual Official Contact List for complete contact information.

15.3.3.1. Deaths

Death is an outcome of an event. The event that resulted in death should be recorded on the appropriate eCRF. All causes of death must be reported as SAEs within 24 hours of the site becoming aware of the event. The Investigator should make every effort to obtain and send death certificates and autopsy reports to IQVIA Pharmacovigilance. The term death will be reported as an SAE only if the cause of death is not known and cannot be determined.

15.3.4. Suspected Unexpected Serious Adverse Reactions

Suspected unexpected serious adverse reactions (SUSARs) are SAEs that are unexpected and judged by the Investigator or Sponsor to be related to the study treatment administered.

Sponsor or designee will report SUSARs to the appropriate regulatory authorities and Investigators as required, according to local law.

15.4. Procedures for Handling Special Situations

15.4.1. Contraception

No animal reproductive studies have been done with rFVIIIFc. The effects of rFVIIIFc on pregnancy or the offspring of male subjects are unknown. In accordance with regulatory guidance, Sponsor recommends that Investigators discuss the use of contraception with subjects, as appropriate.

For Canada specific changes: See Appendix B.

15.4.2. Reporting Pregnancy

Congenital abnormalities/birth defects in the offspring of male subjects will be reported as an SAE when study treatment-exposed conception occurs.

Pregnancy in male subject's partner shall be reported to IQVIA Pharmacovigilance (at the country-specific fax numbers provided in the Study Reference Manual) promptly upon awareness by any study personnel, whether associated with an AE or not. Pregnancy itself will not be considered an AE. In all reported situations, Sponsor or designee will provide the Investigator with a Pregnancy Report Form, which shall be completed and returned by the Investigator. Sponsor or designee will make every effort to follow up on the outcome of the pregnancy.

15.4.3. Overdose

An overdose is any dose of study treatment administered to a subject or taken by a subject that exceeds the dose assigned to the subject according to the protocol. Overdoses are not considered AEs and should not be recorded as an AE on the eCRF; however, all overdoses must be recorded on an Overdose form and faxed to IQVIA Pharmacovigilance within 24 hours of the site becoming aware of the overdose. An overdose must be reported to IQVIA Pharmacovigilance even if it does not result in an AE. If an overdose results in an AE, the AE must be recorded. If an overdose results in an SAE, both the SAE and Overdose forms must be completed and faxed to IQVIA Pharmacovigilance. All study treatment-related dosing information must be recorded on the dosing eCRF.

15.4.4. Medical Emergency

In a medical emergency requiring immediate attention, study site staff will apply appropriate medical intervention, according to current standards of care. The Investigator or designee will contact the study's Medical Monitor. See the Study Reference Manual Official Study Contact List for complete contact information.

15.5. Safety Responsibilities

15.5.1. Investigator Responsibilities

The Investigator's responsibilities include the following (see Section 15.1):

- Monitor and record all AEs, including SAEs, regardless of the severity or relationship to study treatment.
- Determine the seriousness, relationship, and severity of each event.
- Determine the onset and resolution dates of each event.
- Report congenital abnormalities/birth defects in the offspring of male subjects when study treatment-exposed conception occurs.
- Complete an SAE form for each SAE, and fax it to IQVIA Pharmacovigilance within 24 hours of the study site staff becoming aware of the event or new information.
- Ensure that all AE and SAE reports are supported by documentation in the subjects' medical records.
- Pursue AE follow-up information, if possible, until the event has resolved or become stable.
- Report SAEs to local ethics committees, as required by local law.

For Canada specific changes, see Appendix B.

The Investigator may delegate responsibilities for study-related tasks where appropriate to individuals sufficiently qualified by education, training, and experience, in accordance with International Council for Harmonisation (ICH) - Good Clinical Practice (GCP). The Investigator must maintain a list of the appropriately qualified persons to whom significant study-related duties have been delegated.

15.5.2. Sponsor

Sponsor's responsibilities include the following:

- Before study site activation and subject enrollment, the Clinical Monitor or designee is responsible for reviewing with study site staff the definitions of AE and SAE, as well as the instructions for monitoring, recording, and reporting SAEs.
- Sponsor is to notify all appropriate regulatory authorities, central ethics committees, and Investigators of SAEs, as required by local law, within required time frames.

16. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

The objectives of the study and the endpoints to be analyzed are listed in Section 6.

Detailed methodology for summary and statistical analyses of the data collected in this study will be documented in a Statistical Analysis Plan (SAP). In general, continuous variables will be summarized by descriptive statistics, which includes the number, mean, median, standard deviation, minimum, and maximum. Categorical variables and response variables will be presented with the number and percentage in each category. Unless otherwise indicated, analysis will be performed separately for the ITI, Tapering, and Follow-Up Periods. No formal statistical hypothesis testing using inferential statistics will be performed.

16.1. Sample Size Considerations

Because the number of subjects who have severe hemophilia A and developed inhibitors is small, the determination of sample size for this study is constrained by the availability of subjects. To describe the duration of time needed to develop tolerization from the onset of ITI, the study plans to prospectively enroll up to 17 subjects who are to receive ITI for the first time.

16.2. Efficacy

16.2.1. Analysis Populations

For the purpose of statistical analyses, 3 analysis sets are defined based on the following criteria:

- ITI Full Analysis Set (ITIFAS): This set will include all subjects receiving at least 1 infusion 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 subjects entering the tapering phase of the study. All analyses describing efficacy and safety during this phase will be based on this analysis set.
- Follow-Up Period Full Analysis Set: This set will include all subjects entering the follow-up phase in the study. All analyses describing efficacy and safety during this phase will be based on this analysis set.

16.2.2. Methods of Analysis

16.2.2.1. Primary Endpoint Analysis

The primary endpoint of this study, time to tolerization with a maximum of 12 months (48 weeks) of ITI treatment, will be summarized descriptively using minimum, mean, standard deviation, median, 25th and 75th quartiles, and maximum. A Kaplan-Meier plot showing percentage of subjects who are tolerized against time from the first ITI infusion will also be generated. Subjects not achieving ITI success during the 12-month (48-week) ITI Period will be censored at the last observed time for this analysis. The ITIFAS will be used for this analysis.

Descriptive statistics of the levels of rFVIIIFc inhibitors will be summarized longitudinally for all visits during the ITI Period.

16.2.2.2. Secondary Endpoints Analysis

ITI success

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

The ITIFAS will be used for this analysis.

Occurrence of relapse after successful ITI

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

Time to relapse will be defined as the duration between ITI success and time of relapse. Time to relapse from successful ITI will also be summarized descriptively for subjects who relapsed during the Tapering or Follow-Up Period.

Number of bleeding episodes during ITI, Tapering, and Follow-Up Periods

The number of bleeding episodes during ITI will be summarized by month using the ITIFAS. Descriptive statistics for annualized bleeding rate over both Tapering and Follow-Up Periods will also be summarized using the TPFAS. The rate for each subject will be annualized to account for potential difference in Tapering and Follow-Up Periods.

Number of days away from work or school

Number of days missed from school or work will be summarized descriptively for the ITI Period using the ITIFAS and for the combined Tapering and Follow-Up Periods using the TPFAS.

Number of hospitalization days

Number of hospitalization days will be summarized descriptively for the ITI Period using the ITIFAS and for the combined Tapering and Follow-Up Periods using the TPFAS.

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 EPD versus the prescribed doses and percentage of number of days with infusions as registered in the EPD compared with the prescribed number of days will be summarized using descriptive statistics for each of the 3 periods separately.

Consumption during ITI

Consumption during the entire study will be summarized descriptively using the ITIFAS. Descriptive statistics will also be provided for each of the periods separately using their respective analysis set.

16.2.2.3. Pharmacokinetics

Data listings based on local and central laboratory results of IR and/or $t_{½}$ for each subject by visit will be provided.

16.2.2.4. Exposure and Duration of Treatment

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

16.2.2.5. Demography and Baseline Disease Characteristics

Demographics and baseline characteristics will be summarized with descriptive statistics.

16.3. Interim Analyses

An interim analysis is planned for when at least 10 subjects have completed at least 24 weeks (6 months) of ITI treatment. Subsequent interim analyses will depend on the number of years required to recruit the targeted number of subjects.

16.4. Safety

16.4.1. Analysis Populations

See Section 16.2.1.

16.4.2. Methods of Analysis

16.4.2.1. Adverse Events

Reported AEs during the study will be coded using Medical Dictionary for Regulatory Activities. The number and percentage of subjects with any AEs occurring after the first infusion of rFVIIIFc will be summarized in frequency tables by body system, preferred term, and maximum severity. Listings of serious SAEs and AEs leading to discontinuation will also be presented.

Tabulations of AEs and SAEs will be made separately for the ITI Period, the Tapering and Follow-Up Periods combined, as well as all 3 periods combined using ITIFAS and TPFAS, respectively. Tabulation for all AEs by relatedness across all periods will also be presented.

16.4.2.2. Clinical Laboratory Results

Listings of abnormal laboratory test results will be provided.

16.4.2.3. Vital Signs

Vital signs will be summarized by the number and percentage of subjects with clinically relevant abnormalities. Abnormal values will be defined in the SAP. A listing of abnormal vital signs will be provided.

16.5. Subgroup Analysis

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

17. ETHICAL REQUIREMENTS

Sponsor and the Investigator must comply with all instructions, regulations, and agreements in this protocol and applicable ICH-GCP guidelines and conduct the study according to local regulations.

The Investigator may delegate responsibilities for study-related tasks where appropriate to individuals sufficiently qualified by education, training, and experience, in accordance with applicable ICH-GCP guidelines. The Investigator must maintain a list of the appropriately qualified persons to whom significant study-related duties have been delegated.

17.1. Declaration of Helsinki

This study will be performed in alignment with the ethical principles outlined in the Declaration of Helsinki.

17.2. Ethics Committee

The Investigator must obtain ethics committee approval of the protocol, ICF, and other required study documents prior to starting the study. The Sponsor may submit documents on behalf of the investigational sites in countries other than the USA.

If the Investigator makes any changes to the ICF, Sponsor must first approve the changes before the ICF is submitted to the ethics committee. A copy of the approved ICF must be provided to Sponsor. After approval, the ICF must not be altered without the agreement of the relevant ethics committee and Sponsor.

It is the responsibility of the Investigator(s) to ensure that all aspects of institutional review are conducted in accordance with current governmental regulations.

Sponsor must receive a letter documenting ethics committee approval, which specifically identifies the protocol, tracking number, and ICF version, prior to the initiation of the study. Protocol amendments will be subject to the same requirements as the original protocol.

A progress report must be submitted to the ethics committee at required intervals and not less than annually. Documentation of the submission must be provided to Sponsor.

At the completion or termination of the study, the investigational site must submit a close-out letter to the ethics committee and Sponsor.

17.3. Subject Information and Consent

Prior to performing any study-related activities under this protocol, including Screening tests and assessments, written informed consent with the approved ICF must be obtained from the subject or subject's legally authorized representative, as applicable, in accordance with local practice and regulations.

The background of the proposed study, the procedures, the benefits and risks of the study, and that study participation is voluntary for the subject must be explained to the subject (or the

subject's legally authorized representative). The subject must be given sufficient time to consider whether to participate in the study.

Subjects will be informed that their race and ethnicity will be collected and will be used during analysis of study results (unless not able to be reported due to local regulations) (see Section 17.4).

In addition, pediatric subjects who have the capacity should provide their assent to participate in the study. The level of information provided to subjects should match their level of understanding as determined by the Investigator and in accordance with applicable regulations and guidelines.

A copy of the signed and dated ICF (and assent, if applicable) must be given to the subject or the subject's legally authorized representative. Confirmation of a subject's informed consent must also be documented in the subject's medical record prior to any testing under this protocol, including Screening tests and assessments.

Local regulations must be complied with in respect to the final disposition of the original (wet signature) ICF and of copies of the signed and dated ICFs. The original signed ICF will be retained with the study records.

17.4. Subject Data Protection

Prior to any testing under this protocol, including Screening tests and assessments, candidates must also provide all authorizations required by local law (e.g., protected health information authorization in North America).

During the study, the subjects' race and ethnicity will be collected. In cross sectional analyses of different ethnic groups, differences in the occurrence of inhibitors have been observed (Astermark et al., 2005; Carpenter et al., 2012). Differential responses to FVIII products may occur in different haplotypes of FVIII that also differ across racial and ethnic groups (Viel et al., 2009).

Study reports will be used for research purposes only. The subject will not be identified by name in eCRFs, study-related forms, study reports, or any related publications. Sponsor, its partners and designees, ethics committees, and various government health agencies may inspect the records of this study. Every effort will be made to keep the subject's personal medical data confidential.

17.5. Compensation for Injury

Sponsor maintains appropriate insurance coverage for clinical studies and will follow applicable local compensation laws.

17.6. Conflict of Interest

The Investigators will address any potential conflicts of interest (e.g., financial interest in the Sponsor) with the subject before the subject decides to participate in the study.

17.7. Registration of Study and Disclosure of Study Results

Sponsor will register the study and poststudy results regardless of outcome on a publicly accessible website in accordance with applicable laws and regulations.

18. ADMINISTRATIVE PROCEDURES

18.1. Study Site Initiation

The Investigator must not screen any subjects prior to completion of a study initiation visit, conducted by Sponsor or designee and written approval to begin screening. The initiation visit will include a detailed review of the protocol and study procedures.

18.2. Quality Assurance

During and/or after completion of the study, quality assurance officers named by Sponsor or the regulatory authorities may wish to perform on-site audits. The Investigator will be expected to cooperate with any audit and to provide assistance and documentation (including source data) as requested.

18.3. Monitoring of the Study

Sponsor or its designee will conduct on-site visits at the study facilities to monitor various aspects of the study. The Investigator must agree to Sponsor-authorized personnel having direct access to subject (or associated) files to verify entries made in the eCRF. Adequate space and time for monitoring visits must be made available by the Investigator or study staff. The site must complete the eCRFs in a timely manner and on an ongoing basis to allow regular review by the study team.

18.4. Study Funding

This study is designed and financed by Sobi and Bioverativ as part of their collaboration agreement. Bioverativ is the Sponsor of the study and is funding the study with Sobi. All financial details are provided in the separate contract(s) between the institution, Investigator, and Sponsor.

18.5. Publications

Details are included in the clinical trial agreement for this study.

19. FURTHER REQUIREMENTS AND GENERAL INFORMATION

19.1. External Contract Organizations

19.1.1. Contract Research Organization

A CRO will be responsible for the administrative aspects of the study including, but not limited to, study initiation, monitoring, and management of SAE reports, and data management. Before subjects are screened at each study site, the CRO will review study responsibilities with the Investigators and other study site staff, as appropriate.

19.1.2. Interactive Web Response System

An IXRS will be used in this study. Before subjects are screened or enrolled, the IXRS vendor will provide each study site with the necessary training, a user manual, and access rights to the system.

19.1.3. Electronic or Remote Data Capture

Subject information will be captured and managed by study sites on eCRFs by a Web-based electronic data capture (EDC) tool developed and supported by the CRO assisting with the conduct of the study and configured by Sponsor. It is recommended that data be entered into the EDC tool within 5 business days, including batched records and records with source documents.

Subjects and/or his parents/caregivers in the study will have EPDs to record information regarding each dose of rFVIIIFc administered to the subject for any reason. EPD data must be entered within 7 days (see Section 13.1.4.2). Entries will be made in EPD for at-home administration and in the eCRF for in-clinic/scheduled visit administration.

19.1.4. Central Laboratory for Assessments

Laboratory samples will be drawn for assessment of inhibitor titer (Nijmegen-modified Bethesda assay or Bethesda assay at sites that have not yet adopted the Nijmegen-modified assay), FVIII activity (1-stage aPTT assay) for IR and $t_{½}$, immune cell characterization, viral analysis, optional analysis of FVIII mutation and HLA allotyping. These samples will be analyzed at the local laboratory and the central laboratory. The Investigators will use local laboratory results for purposes of decision-making.

19.2. Study Committees

Not applicable.

19.3. Changes to Final Study Protocol

All protocol amendments must be submitted to the ethics committee and Regulatory Authorities if required by local law. Protocol modifications that affect subject safety, the scope of the investigation, or the scientific quality of the study must be approved by the ethics committee before implementation of such modifications to the conduct of the study. If required by local

law, such modifications must also be approved by the appropriate regulatory agency prior to implementation.

However, Sponsor may, at any time, amend this protocol to eliminate an apparent immediate hazard to a subject. In this case, the appropriate regulatory authorities will be notified after the amendment.

In the event of a protocol modification, the subject consent form may require similar modifications (see Section 17.3).

19.4. Ethics Committee Notification of Study Completion or Termination

Where required, the health authorities and ethics committees must be notified of completion or termination of this study and sent a copy of the study synopsis in accordance with necessary timelines.

19.5. Retention of Study Data

The minimum retention time for study records will meet the strictest standard applicable to that site, as dictated by any institutional requirements or local laws or regulations. Prior to proceeding with destruction of records, the Investigator must notify Sponsor in writing and receive written authorization from Sponsor to destroy study records. In addition, the Investigator must notify Sponsor of any changes in the archival arrangements including, but not limited to, archival at an off-site facility or transfer of ownership if the Investigator leaves the site.

19.6. Study Report Signatory

Sponsor will designate one of the participating Study Investigators as a signatory for the study report. This determination will be made by several factors, including, but not limited to, the Investigator's experience and reputation in the studied indication; the Investigator's contribution to the study in terms of design, management, and/or subject enrollment; or by other factors determined to be relevant by Sponsor.

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21. INVESTIGATORS SIGNED AGREEMENT OF STUDY PROTOCOL

I have read the foregoing protocol, "A Non-Controlled, Open-Label, Multicenter, Study of Efficacy of rFVIIIFc for Immune Tolerance Induction (ITI) in Severe Hemophilia A Subjects With Inhibitors Undergoing the First ITI Treatment" and agree to conduct the study according to the protocol and the applicable ICH-GCP guidelines and local regulations, and to inform all who assist me in the conduct of this study of their responsibilities and obligations.

_____

Investigator's Signature Date

_____

Investigator's Name (Print)

_____

Study Site (Print)

APPENDIX A. PROTOCOL AMENDMENT HISTORY

The "Protocol Amendment Summary of Changes Table" for the current amendment is located at the start of this document (after title page).

The primary reason for this amendment to Protocol 997HA402 (version 3.0) is to reduce the number of subjects to be enrolled, to clarify the timing for subjects moving from interim ITI visits to ITI outcome assessment visits, and to clarify sample collection schedules for ADA. Additional updates have been made for Canada and these country-specific changes are outlined in Appendix B.

Previous global and country-specific amendments are outlined below.

Protocol Version 1.1 (specific for Canada)

Protocol Version 1.1 (from Version 1.0)	New texts were added to the following sections: Section 8.1, Section 15.5.1	The primary reason for this amendment to Protocol 997HA402 was to add the Inclusion Criterion #5 in response to Health Canada Question #2 dated 26 June 2017. The Canadian regulatory authority requested addition of a requirement for study participants to use effective contraception, as it is not known whether ELOCTATE can affect fertility or sperm development in hemophilia A patients.This was addressed by adding Inclusion Criterion #5. This change also affected the Informed Consent Form, which has been updated accordingly. The amendment summary describing every change is available upon request.

Protocol Version 2.0 (Global, except Canada)

Protocol Version 2 (from Version 1.0)	The changes were introduced in the following sections: Synopsis, Section 4.1, Section 4.2.1, Section 5, Section 6.1, Section 6.2, Section 6.3, Section 7, Section 8.1, Section 8.2, Section 9.1, Section 9.2, Section 11, Section 12.1, Section 13, Section 14, Section 15, Section 16, Section 17, Section 18, Section 19, and in Table 1, Table 2, Table 3 and new Section 7.2.2.1, Section 7.2.2.2 and Section 7.2.3 have been added.	The primary reason for this amendment to Protocol 997HA402 was to provide further clarifications, consistency, and a few corrections. The amendment summary describing every change is available upon request.

Protocol Version 2.1 (specific for Canada)

Protocol Version 2.1 (from Version 1.1)	The changes were introduced in the following sections/tables: Synopsis, Section 4.1, Section 4.2.1, Section 5, Section 6.1, Section 6.2, Section 6.3, Section 7, Section 8.1, Section 8.2, Section 9.1, Section 9.2, Section 11, Section 12.1, Section 13, Section 14, Section 15, Section 16, Section 17, Section 18, Section 19, and in Table 1, Table 2, Table 3 and new sections, Section 7.2.2.1, Section 7.2.3, Section 13.1.2.1, Section 13.1.2.2, Section 13.1.3.1, Section 13.1.3.2, Section 13.5.5, Section 15.4.1, Section 16.3 have been added.	The primary reason for this amendment to Protocol 997HA402 was to provide further clarifications, consistency, and a few corrections, consistent to changes for Version 2.0 The amendment summary describing every change is available upon request.

APPENDIX B. COUNTRY SPECIFIC REQUIREMENTS

Country-specific requirements for Canada

Compared to the global prolocol, the country specific changes for Canada are underlined (for aditions) or skriked out (for deletions).

1. Changes in Protocol Version 3

Section 4.2 (Table 1, footnote 7) and Section 13.5.4

This assessment is optional, and requires a separate ICF. For subjects whose FVIII mutation and human leukocyte antigen (HLA) allotype is not documented in medical records, ~~samples for~~ analysis of FVIII mutation and HLA allotyping will be offered. If subject or subject's legally authorized representative consents, samples for analysis will ~~To~~ be collected at the Baseline Visit or at any subsequent visit if blood volume is limited at the Baseline Visit for analysis at the central laboratory.

Section 4.2 (Table 2, footnote 1)

During the Tapering and Follow-Up Periods, the subject's dose will be adjusted to achieve each subject's prophylactic dose as determined by the Investigator. Minimum Tapering Period is 16 weeks (4 months). Subjects who relapse during the Tapering Period (i.e., who have confirmation of inhibitor development AND who have confirmed decrease of IR, with or without clinical signs or symptoms) will proceed immediately to the EOT Visit where $t_{1/2}$ will be assessed and recorded. Subjects will be closely monitored during the Tapering Period for potential relapse.

Section 14.2

Clinically significant abnormal laboratory values should be reported as AEs. ~~at the discretion of the Investigator~~. The corresponding result should be entered into the eCRF together with information on laboratory variable assessed, date of sample, and normal range from the local laboratory.

2. Changes from Protocol Version 2.1

Section 15.4.1

No animal reproductive studies have been done with rFVIIIFc. The effects of rFVIIIFc on pregnancy or the offspring of male subjects are unknown. ~~In accordance with regulatory guidance, Sponsor recommends that~~ Investigators must discuss the use of contraception with subjects~~, as appropriate~~.

If the subject is fertile and has a female partner of childbearing potential, the subject and partner must use effective contraception during the study and continue contraception for 7 days after his last dose of study treatment. The study participant must not donate sperm during the study and for 7 days after his last dose of study treatment.

3. Changes from Protocol Version 1.1

Section 8.1

To be eligible to participate in this study, candidates must meet the following eligibility criteria at the time of enrollment:

1. Ability of the subject or his legally authorized representative (e.g., parent or legal guardian) to understand the purpose and risks of the study and provide signed and dated informed consent and authorization to use protected health information in accordance with national and local subject privacy regulations
2. Male subjects of any age diagnosed with severe hemophilia A (as confirmed from the medical record)
3. Currently diagnosed with high-titer inhibitors (historical peak ≥5 BU/mL, according to medical records)
4. Previously treated with any pd-FVIII or recombinant conventional or Extended Half-Life FVIII
5. If the subject is fertile and has a female partner of childbearing potential, the subject and partner must use effective contraception during the study and continue contraception for 7 days after his last dose of study treatment. The study participant must not donate sperm during the study and for 7 days after his last dose of study treatment.

Section 15.5.1

- Monitor and record all AEs, including SAEs, regardless of the severity or relationship to study treatment.
- Determine the seriousness, relationship, and severity of each event.
- Determine the onset and resolution dates of each event.
- Report congenital abnormalities/birth defects in the offspring of male subjects when study treatment-exposed conception occurs.
- Report pregnancy in the partner of a male subject when study-treatment-exposed conception occurs, whether or not the pregnancy is associated with an AE.
- Complete an SAE form for each SAE, and fax it to IQVIA Pharmacovigilance within 24 hours of the study site staff becoming aware of the event or new information.
- Ensure that all AE and SAE reports are supported by documentation in the subjects' medical records.
- Pursue AE follow-up information, if possible, until the event has resolved or become stable.
- Report SAEs to local ethics committees, as required by local law.