Bioverativ

PROTOCOL NUMBER: 997HA306

PHASE OF DEVELOPMENT: 3

Bioverativ Therapeutics Inc.
225 Second Avenue
Waltham, MA 02451
United States

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

EUDRA CT NO: 2013-005512-10

DATE: 12 February 2018
Version 6
FINAL

Supersedes previous Version 5 dated 23 February 2017

SPONSOR SIGNATURE

Protocol 997HA306 was approved by:

15FEB18

Date

Bioverativ Therapeutics Inc.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

1. SPONSOR INFORMATION

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

Bioverativ Therapeutics Inc.
225 Second Avenue
Waltham, MA 02451

Phone: [redacted]
Fax: [redacted]

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

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

2. LIST OF ABBREVIATIONS

ABR	annualized bleeding rate
ADR	adverse drug reaction
AE	adverse event
aPCC	activated prothrombin complex concentrate
aPTT	activated partial thromboplastin time
BU	Bethesda unit
CHMP	Committee for Medicinal Products for Human Use
CI	confidence interval
CL	clearance
CRO	contract research organization
DHA	Directions for Handling and Administration
DLT	dose-limiting toxicity
DNAUC	dose-normalized area under the curve
DSMC	Data Safety Monitoring Committee
eCRF	electronic case report form
ED	exposure day
EMA	European Medicines Agency
EOS	End of Study
EOT	End of Treatment
EPD	electronic patient diary
ET	early termination
F8	target gene for hemophilia A
FAS	Full Analysis Set
FcRn	neonatal Fc receptor
FVIII	coagulation factor VIII
FVIII:C	coagulation activity of coagulation factor VIII in plasma
GCP	Good Clinical Practice
HIV	human immunodeficiency virus
ICF	informed consent form
ICH	International Council for Harmonisation
IgG1	immunoglobulin G1
IR	incremental recovery
ITI	immune tolerance induction
IV	intravenous
IU	international units
IXRS	Interactive Voice/Web Response System
MRT	mean residence time
PHI	protected health information
PK	pharmacokinetic(s)
PTP	previously treated patient
PUP	previously untreated patient

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
V_{ss}	volume of distribution at steady state
WHO	World Health Organization

3. SYNOPSIS

This is a brief summary. For details refer to the body of the protocol.

Protocol Number:	997HA306
Protocol Title:	An Open-Label, Multicenter Evaluation of the Safety and Efficacy of Recombinant Coagulation Factor VIII Fc Fusion Protein (rFVIIIFc; BIIB031) in the Prevention and Treatment of Bleeding in Previously Untreated Patients With Severe Hemophilia A
Version Number:	6
Name of Study Treatment:	Antihemophilic Factor, Recombinant Coagulation Factor VIII Fc Fusion Protein (rFVIIIFc; BIIB031)
Study Indication:	Hemophilia A
Phase of Development:	3
Rationale for the Study:	The use of a prophylaxis regimen in young children starting prior to the onset of frequent joint bleeding is currently the recommended standard of care in hemophilia due to the demonstrated benefit on long-term outcomes [Aznar 2000; Manco-Johnson 2007; Molho 2000]. Currently available coagulation factor VIII (FVIII) replacement therapies are limited by short elimination half-life ($t_{½}$). The purpose of this study is to investigate the safety and efficacy of rFVIIIFc in previously untreated patients (PUPs) in accordance with the European Medicines Agency (EMA) Committee for Medicinal Products for Human Use (CHMP) guideline on the clinical investigation of recombinant and human plasma-derived factor VIII products [EMA (EMA/CHMP/BPWP/144533/2009) 2011].
Study Objectives and Endpoints:	**Objectives** Primary: The primary objective of the study is to evaluate the safety of rFVIIIFc in previously untreated subjects with severe hemophilia A. Secondary:

The secondary objectives of the study are as follows:

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

The exploratory objectives of the study are

- To evaluate the effect of rFVIIIFc based on patient-reported outcomes and health resource utilization
- To assess the efficacy of rFVIIIFc for perioperative management

Endpoints

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

The secondary endpoints of the study are as follows:

- The annualized number of bleeding episodes per subject.
- The annualized number of spontaneous joint bleeding episodes per subject.
- The number of injections and dose per injection of rFVIIIFc required to resolve a bleeding episode.
- Assessments of response to treatment with rFVIIIFc for bleeding episodes, using the 4-point bleeding response scale.
- The total number of exposure days (EDs) per subject per year.

- Total annualized rFVIIIFc consumption per subject for the prevention and treatment of bleeding episodes.
- rFVIIIFc incremental recovery (IR)
- Response to ITI with rFVIIIFc (complete success, partial success, failure, early withdrawal)

Exploratory endpoints in the study include, but are not limited to

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

Study Design:

An open-label, single-arm, multicenter study evaluating the safety and efficacy of rFVIIIFc in previously untreated pediatric subjects with severe hemophilia A when used according to local standard of care for implementation of a prophylaxis regimen, including an optional preceding episodic (on-demand) treatment regimen. The duration of episodic treatment is at the Investigator's discretion, in accordance with local standard of care. Surgery is allowed during the study. ITI is allowed during the study for subjects developing a positive inhibitor after exposure to rFVIIIFc. Separate consent is required before starting an ITI regimen. For subjects with inhibitors, the end of treatment will be defined based on the outcome of ITI therapy and the completion of any required tapering regimen and monitoring periods. The study will end after at least 90 subjects have reached at least 50 EDs with rFVIIIFc.

Subjects may be enrolled and receive study drug after samples for factor VIII activity and inhibitor testing at the central laboratory have been drawn, and diagnosis of severe hemophilia A with less than 1% factor VIII activity has been established based on local labs. However, any such subject must be withdrawn if the central laboratory screening results indicate factor VIII activity ≥1%, or a positive inhibitor.

Rationale for Dose and Schedule Selection:

In the completed Phase 3 study (Study 997HA301) multiple doses of up to 65 IU/kg were well tolerated, with an adverse event (AE) profile generally consistent with that expected in patients with hemophilia A. Safety data from the completed

pediatric study in subjects <12 years of age (Study 8HA02PED), which allowed for doses up to 80 IU/kg and a minimum dosing interval of 2 days, showed a safety profile generally consistent with the results of the Phase 3 study.

The dose for initiation of prophylaxis may be chosen by the Investigator within the range of 25 to 80 IU/kg. The dose can be adjusted based on the subject's response to dosing in the range of 25 to 65 IU/kg at 3 to 5 day intervals. Adjustments to the dose and interval of rFVIIIFc can be made in this study based on available PK data including FVIII activity levels, level of physical activity, and bleeding pattern, in accordance with local standards of care for a prophylactic regimen. Based on data from the completed clinical studies, and knowledge of increased clearance of factor concentrates in children <6 years of age, more frequent or higher doses of up to 80 IU/kg may be required.

The dose for treatment of bleeding episodes will target peak plasma FVIII activity of approximately 40% to 100%, in accordance with local standards.

Subjects will be eligible to undergo ITI with rFVIIIFc if

- They develop a positive high titer inhibitor (≥5.00 Bethesda Units [BU]/mL)

or

- They develop a positive low titer inhibitor (≥0.60 and <5.00 BU/mL) and experience poorly controlled bleeding despite increased rFVIIIFc doses, or require bypassing agents to treat bleeding.

The ITI regimen will approximate the high-dose treatment arm of the International ITI Study protocol, and will utilize single injections of rFVIIIFc at a dose of 200 IU/kg, daily, consistent with current ITI guidelines [Valentino 2015]. This dosing regimen is also supported by the results of a prospective clinical trial 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 and 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

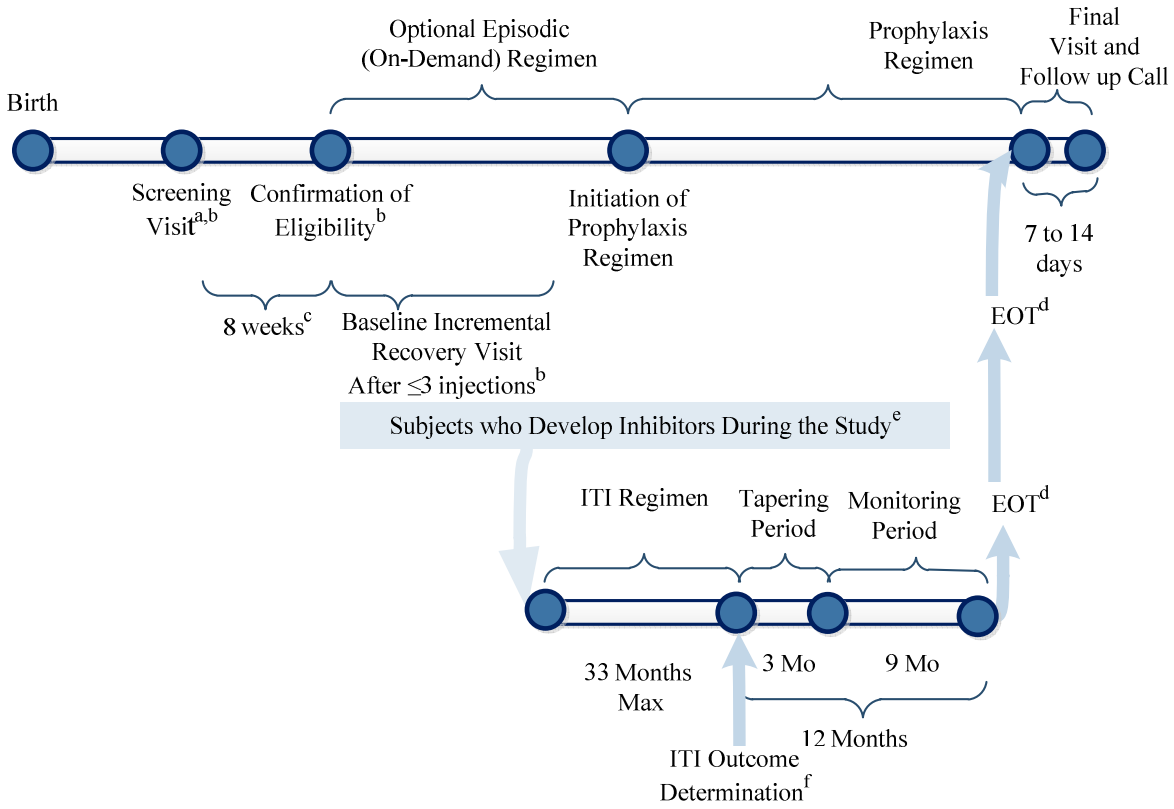
	of FVIII, compared to subjects treated with the low dose. Furthermore, subjects treated with the high dose for ITI had a lower rate of intercurrent bleeding and fewer hospitalizations due to bleeding than subjects treated with the low dose. Since clearance is expected to be very rapid in the presence 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 maximize the potential for rapid tolerization while minimizing bleeding-related adverse events.
Study Location:	Multinational
Number of Planned Subjects:	At least 90 pediatric PUPs are expected to reach at least 50 EDs with rFVIIIFc at the end of the study.
Study Population:	This study will be conducted in male, previously untreated subjects <6 years of age with severe hemophilia A. Detailed entry criteria are described in the protocol.
Treatment Groups:	This is a single-arm study. Subjects who develop inhibitors after exposure to rFVIIIFc study drug may meet additional criteria that make them eligible for treatment with an ITI regimen on the study.
Duration of Treatment and Follow-up:	Individual subject study participation is expected to be approximately 6 months to 3 years including screening and follow-up. For each subject, the treatment period is no less than 50 EDs to the study treatment, unless the subject develops an inhibitor or the end of study (EOS) is declared.
Statistical Methods:	In general, all statistical analyses will be descriptive in nature. No formal comparison is planned, and no hypothesis will be formally tested. Continuous variables will be summarized and presented by the number of observations, mean, median, standard deviation, minimum, and maximum. Categorical variables will be summarized by the number and percentage in each category. Subjects with at least 1 dose of rFVIIIFc will be included in the Full Analysis Set (FAS) and the Safety Analysis Set. Efficacy analyses will be based on the FAS, and safety analyses will be based on the Safety Analysis Set. Subjects developing a confirmed positive inhibitor test after exposure to rFVIIIFc study drug will have their efficacy and safety

	data included up to the time of the last negative inhibitor test; efficacy and safety data collected after the time of the last negative inhibitor test will be summarized separately. Summary statistics will be presented for safety and efficacy endpoints. The proportion of subjects developing inhibitors will be presented with a 95% confidence interval. For efficacy purposes, the number of bleeding episodes will be annualized. The summary statistics of annualized bleeding episodes and the subject's response to treatment will be presented separately for episodic and prophylaxis treatment. Other statistical analyses may be conducted for exploratory purposes.
Interim Analysis:	An interim analysis of safety and efficacy data will be conducted when at least 50 subjects have completed at least 50 EDs and undergone inhibitor testing. Additional interim analyses may be conducted during the study, as needed. Analyses will be descriptive in nature. No formal comparisons are planned, and no hypotheses will be formally tested.
Sample Size Determination:	Because the size of the hemophilia population is limited, the sample size is based on clinical rather than statistical considerations. Taking into account the CHMP Guideline [EMA (EMA/CHMP/BPWP/144533/2009) 2011] and in an effort to enroll a sufficient number of subjects to assess the efficacy and safety of rFVIIIFc in this population of primarily very young children, approximately 105 subjects will be dosed with rFVIIIFc to achieve at least 90 subjects with no less than 50 EDs by the completion of the study.
Study Stopping Rules:	Study stopping is required for the following: • Unacceptable inhibitor incidence as advised by the Data Safety Monitoring Committee (DSMC). • Detection of an unexpected, serious, or unacceptable risk to the study subjects.

4. STUDY SCHEMATIC AND SCHEDULE OF ACTIVITIES FOR STUDY 997HA306

4.1. Study Schematic

Figure 1: Study Design



EOT = End of Treatment; ET = Early Termination; ITI = immune tolerance induction
[a] Subjects may not enter the study if they have received any injections of factor prior to the Confirmation of Eligibility.
[b] Screening Visit and Baseline Incremental Recovery Visit may be performed as 2 separate visits OR all activities necessary for screening, confirmation of eligibility, and the baseline incremental recovery visit may be performed at the same visit.
[c] If screening assessments cannot be completed within 8 weeks, some assessments may need to be repeated as described in Section 7.3.1.
[d] The most common scenarios for EOT are shown; however, EOT may occur under other circumstances as defined by the protocol, for example, when the End Of Study is declared for the study or upon early withdrawal of a subject. (Section 10.6)
[e] See Section 10.2.5 for criteria.
[f] See the ITI Outcome Algorithm in Figure 2.

4.2. Schedules of Activities

4.2.1. Schedule of Activities: Screening and Baseline Incremental Recovery Visit

Activities	Screening	Baseline Incremental Recovery Visit[a]	
		Predose	Postdose
Informed Consent	X		
Demographics[b]	X		
Medical and Surgical History[c]	X		
Physical Examination	X		
Height	X		
Weight	X	X	
Vital Signs[d]	X	X	X
Health Outcome	X		
Hematology[e]	X		
Blood Chemistry[f]	X		
Viral Analysis[g]	X		
Nijmegen-Modified Bethesda Assay (Inhibitor Assay)[h,i]	X	X[i]	
FVIII Activity[h]	X		
FVIII Activity for Incremental Recovery[j]		X[i]	X
Anti-rFVIIIFc Antibody	X	X[i]	
F8 Genotyping[k]		X	
Injection Site Inspection			X
EPD Review, including rFVIIIFc Dosing Accountability		Monitor and record at all visits	
rFVIIIFc Clinic Dosing		X	
Assessment of Response in EPD by Parent/Caregiver[l]		Monitor and record at all visits	
Physician's Assessment of Response to Individual Bleeding Episodes Treated in Clinic		Monitor and record at all visits	
Adverse Events[m]		Monitor and record at all visits	
Serious Adverse Events[n]	X	Monitor and record at all visits	
Concomitant Therapy/ Procedures Recording[o]	X	Monitor and record at all visits	

AE = adverse event; DHA=Directions for Handling and Administration; ED = exposure day; EPD = electronic patient diary; ET = Early Termination; F8 = target gene for hemophilia A; FVIII = coagulation factor VIII; HIV = human immunodeficiency virus; ICF = informed consent form; IR = incremental recovery; rFVIIIFc = recombinant coagulation factor VIII Fc fusion protein; SAE = serious adverse event.

[a] The Baseline IR Visit activities may be completed on the same day as Screening, or they may be completed as a

part of a separate visit as shown. Baseline IR requires a washout from rFVIIIFc of at least 24 hours prior to the predose sample collection.

[b] Race and ethnicity will be included among the demographic data collected in this study, for reasons described in Section 17.4.

[c] Medical and surgical history includes any significant medical condition and/or any significant surgical histories, plus the following: HIV infection status (if positive, viral load, cluster of differentiation 4 [CD4] count, and platelets; based on laboratory results within the last 6 months), hepatitis B infection status, hepatitis C infection status, medication history, and any other congenital immunodeficiency. Medical history should also include any exposure to blood components or other factor replacement products prior to Screening and the time when the subject meets all eligibility criteria, since these would exclude the subject.

[d] Vital signs include blood pressure, pulse rate, respiratory rate, and temperature (°C). Postdose assessments following in-clinic injections should be taken approximately 20 minutes after the end of the rFVIIIFc injection.

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

[f] 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.

[g] Sample to be used to determine seropositivity at Screening, should subject be diagnosed with HIV, hepatitis B, or hepatitis C during the study.

[h] See minimum criteria for enrollment, Section 8.3.

[i] The predose activity, anti-drug antibody, and inhibitor testing are only required for subjects who received at least 1 dose of FVIIIFc (or 1 accidental dose of a factor VIII product) between enrollment and the dose for the baseline IR assessment.

[j] Volume and units of factor infused at Baseline IR must be calculated and recorded using the *actual* potency as described in Section 10.1.1 (and in the DHA). The dose of factor for the IR baseline is 25 IU/kg (Section 10.2.1.1). Blood samples will be taken at trough (predose; 30 minutes prior to the start of the rFVIIIFc injection) and postdose at 30 (±5) minutes after the start of the rFVIIIFc injection.

[k] If genotype is not known and the parent/legal guardian provides separate consent for genotyping, a sample will be drawn for analysis during the Predose Baseline IR Visit. If blood volume is limiting, this assessment may be performed at a subsequent visit (Section 4.2.2.1). The subject's parent/legal guardian may provide consent in order to receive this testing at any time during the Treatment Period.

[l] The subject's parent/caregiver must enter dosing information into the EPD ***as soon as possible after an injection and within a maximum of 7 days*** following the injection (Section 10.2.4.1.4). It is recommended that parents/caregivers enter dosing information immediately after an injection.

[m] AEs are to be monitored and recorded from the time of first dose of rFVIIIFc.

[n] SAEs are to be monitored and recorded from the time of signing informed consent form.

[o] For subjects who are receiving breast milk, maternal concomitant medications will also be collected at the same time points as other concomitant therapies, unless the breast milk is derived from a source other than the mother or the mother has not consented.

4.2.2. Treatment Period Visits

Subjects on episodic or prophylactic treatment in this study will participate in regular interim visits for follow up (Section 4.2.2.1), as well as follow up at specific ED milestones (Section 4.2.2.2). Subjects on ITI will participate in an ITI-specific schedule of interim visits (Section 4.2.2.3, and, if applicable, Section 4.2.2.4 and Section 4.2.2.5). Subjects requiring surgery will also participate in specialized visits (Section 4.2.2.6).

4.2.2.1. Schedule of Activities: Episodic and Prophylaxis Regimens

Interim visits will be scheduled for all of the subjects on this study. Subjects on episodic and prophylaxis regimens will follow the schedule of activities below.

Activities	Interim Visits				ET/ EOT Visit	Final Safety Follow-Up Visit/ Telephone Call[c]
	Episodic Regimen Visits every 12 (±2) weeks[a]		Prophylaxis Regimen Visits every 12 (±2) weeks[b]			
	Predose	Postdose	Predose	Postdose		
Physical Examination	X		X		X	
Height					X	
Weight	X		X		X	
Vital Signs[d]	X	X	X	X	X	
Health Outcome[e]	X		X		X	
Hematology[f]	X		X		X	
Blood Chemistry[g]	X		X		X	
Nijmegen-Modified Bethesda Assay (Inhibitor Assay)[h]	X		X		X[j]	
FVIII Activity[i]			X	X		
Anti-rFVIIIFc Antibody	X		X		X	
F8 Genotyping[j]	If needed					
Injection Site Inspection[k]		X		X	X	
Physician's Global Assessment of Response	X		X			
rFVIIIFc Clinic Dosing[l]	X		X		X	
EPD Review, including rFVIIIFc Dosing Accountability[m,n]	<<<< ONGOING; Monitor and record at all visits; telephone call every month>>>					
Assessment of Response in EPD by Caregiver[m,n]	<<< ONGOING; Monitor and record at all visits; telephone call every month>>>					
Physician's Assessment of Response to Individual Bleeding Episodes Treated in Clinic[k]	<<< ONGOING; Monitor and record at all visits; telephone call every month>>>					
Adverse Events[n,o]	<<< ONGOING; Monitor and record at all visits; telephone call every month>>>					
Serious Adverse Events[n,p]	<<< ONGOING; Monitor and record at all visits; telephone call every month>>>					

Activities	Interim Visits				ET/ EOT Visit	Final Safety Follow-Up Visit/ Telephone Call[c]
	Episodic Regimen Visits every 12 (±2) weeks[a]		Prophylaxis Regimen Visits every 12 (±2) weeks[b]			
	Predose	Postdose	Predose	Postdose		
Concomitant Therapy/ Procedures Recording[q]	<<< ONGOING; Monitor and record at all visits; telephone call every month>>>					

AE = adverse event; DHA=Directions for Handling and Administration; ED = exposure day; EOT = end of treatment; EPD = electronic patient diary; ET = Early Termination; F8 = target gene for hemophilia A; FVIII = coagulation factor VIII; HIV = human immunodeficiency virus; ICF = informed consent form; rFVIIIFc = recombinant coagulation factor VIII Fc fusion protein; SAE = serious adverse event.

[a] For subjects on episodic treatment who have had no infusions of factor since the previous visit, blood draws will only be required every 24 weeks, rather than every 12 weeks.

[b] If an investigator chooses to have the subject temporarily withdraw from treatment with rFVIIIFc and delay the start of ITI, the subject should continue to participate in Interim visits every 12 ± 2 weeks (per the prophylaxis regimen).

[c] A follow-up telephone call or in-person visit is required 7 to 14 days after the last dose of rFVIIIFc to monitor AEs, SAEs, and concomitant medications and procedures.

[d] Vital signs include blood pressure, pulse rate, respiratory rate, and temperature (°C). Assessments for in-clinic injections should be taken prior to and approximately 20 minutes after the end of the rFVIIIFc injection.

[e] Health outcome assessments will be performed every other visit during episodic and prophylaxis regimens, that is, every 24 weeks.

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

[g] 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.

[h] An unscheduled visit may be required to repeat inhibitor testing under this protocol if the ET/EOT Visit inhibitor test is not evaluable or to obtain a sample to confirm a positive inhibitor test result.

[i] Samples for FVIII activity will only be taken if the subject receives an rFVIIIFc injection during the site visit and is in a non-bleeding state. Volume and units of factor infused must be calculated and recorded using the *nominal* strength as described Section 10.1.1 (and in the DHA). Predose sample is to be collected within 30 minutes prior to the start of rFVIIIFc injection; postdose sample is to be taken 30 (±5) minutes after the start of the rFVIIIFc injection.

[j] If the subject's genotype was not already known at Screening and the sample could not be drawn due to blood volume limitations at the Predose Baseline IR Visit, this assessment may be performed at the first Interim Visit. If the subject develops an inhibitor on the study, a sample may be drawn for this testing at any time during the Treatment Period. The parent/legal guardian must provide separate consent for genotyping.

[k] Injection site inspection is to be performed only if the subject receives an rFVIIIFc injection during a clinic visit.

[l] Clinic dosing is applicable only if warranted.

[m] The subject's parent/caregiver must enter dosing information into the EPD ***as soon as possible after an injection and within a maximum of 7 days following the injection*** (Section 10.2.4.1.4). It is recommended that parents/caregivers enter dosing information immediately after an injection.

[n] In addition to scheduled clinic visits, telephone calls are planned approximately once a month for study site staff to check on each subject's status. During the monthly phone call, the subject's parent/caregiver will also be reminded about the requirement for timely EPD data entry, and assessments of "spontaneous" and "traumatic" bleeds will be noted.

[o] AEs to be monitored and recorded from the time of first dose of rFVIIIFc.

[p] SAEs to be monitored and recorded from the time of signing ICF.

[q] For subjects who are receiving breast milk, maternal concomitant medications will also be collected at the same

time points as other concomitant therapies, unless the breast milk is derived from a source other than the mother or the mother has not consented.

4.2.2.2. Schedule of Activities: Exposure Day Milestone Visits

In addition to the assessments at the interim visits described in Section 4.2.2.1, subjects must undergo testing for inhibitors at the ED milestones shown below. Testing for inhibitors may be combined with a scheduled interim visit. However, if an interim visit does *not* occur within the time windows below, the subject must return to the clinic to have the samples collected. In addition, if inhibitor development is suspected at any time during the study (e.g., the expected plasma factor VIII activity levels are not attained or if bleeding is not controlled with an expected dose), the subject will be tested for inhibitors by the central laboratory.

	Visits at			
Activities	**5 ED (5±1 ED)**	**10 ED (10 to 15 ED)**	**20 ED (20 to 25 ED)**	**50 ED (50 to 55 ED)**
Nijmegen-Modified Bethesda Assay (Inhibitor Assay)	X	X	X	X

ED = exposure day

4.2.2.3. Schedule of Activities: Immune Tolerance Induction

The following schedule applies to subjects who are eligible for ITI, as described in Section 10.2.5.2. The specific follow up tests to be performed following ITI depend on the outcome of ongoing testing as described in Section 10.2.7.4 and Figure 2.

Activities	Pre-ITI Assessment (ITI Day 0)	Week 2 Visit (at 2 wks ±3 days)	ITI Visits		
			Every 4 Weeks (±2 Weeks) ⇨	Every 4 Weeks (±2 Weeks) ⇨	Every 4 Weeks (±2 Weeks)
			Starting at ITI Week 4, Until negative titer is confirmed	Starting at time of confirmed negative titer, Until IR ≥66% of expected is confirmed	Starting at time of IR confirmed ≥66 % Until ITI Complete Success[a] OR 33 Months of treatment
Informed Consent[b]	X				
Physical Examination	X	X	X	X	X
Weight (kg)	X	X	X	X	X
Vital Signs[c]	X	X	X	X	X
Hematology[d,e]	X		X	X	X
Blood Chemistry[e,f]	X		X	X	X
rFVIIIFc Dosing[g]	X	X	X	X	X
Nijmegen-Modified Bethesda Assay (Inhibitor Assay)[h]	X	X	X	X	X
Blood Sample for Exploratory Biomarker Characterization[i]	X		X	X	X
FVIII Activity for Incremental Recovery[j]			X	X	X
Half-life Evaluation (Factor VIII activity only to be done every 12 weeks once IR ≥66% confirmed)[k]					X[l]
Anti-rFVIIIFc Antibody	X	X	X	X	X
EPD Review, including rFVIIIFc Dosing Accountability[m]	X	X	X	X	X
Injection Site Inspection[n]	X	X	X	X	X
Adverse Events	<<<ONGOING; Monitor and record at all visits; telephone call every month>>>				

Serious Adverse Events	<<<ONGOING; Monitor and record at all visits; telephone call every month>>>
Concomitant Therapy/Procedures Recording[o]	<<<ONGOING; Monitor and record at all visits; telephone call every month>>>

AE = adverse event; DHA=Directions for Handling and Administration; EOT = end of treatment; ET = early termination; FVIII = coagulation factor VIII; ITI = immune tolerance induction; rFVIIIFc = recombinant coagulation factor VIII Fc fusion protein; SAE = serious adverse event.

[a] See Section 10.2.7.4.2 for criteria for complete success.
[b] Informed consent must be obtained prior to the ITI assessments beginning at Week 0.
[c] Vital signs include blood pressure, pulse rate, respiratory rate, and temperature (°C). Postdose assessments following in-clinic rFVIIIFc injections should be taken approximately 20 minutes after the end of the injection.
[d] Hematology includes white blood cell count and differential, red blood cell, hemoglobin, hematocrit, and platelet count.
[e] From the start of the ITI treatment period through the time of ITI complete success, samples may be drawn every other month for testing.
[f] 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.
[g] Clinic dosing is applicable only if warranted.
[h] The definitive Nijmegen assay for each timepoint must be performed by the central laboratory.
[i] A whole blood sample will be collected every other month during ITI treatment and at the time when the ITI outcome is declared (complete success, partial success, or failure), for exploratory assays related to immune response during ITI. Up to 10-mL (minimum 3 mL) will be collected, as allowable based on patient weight and institutional practice regarding blood draw restrictions for pediatric patients.
[j] Predose samples for incremental recovery (IR) calculations are to be taken when the subject is in a non-bleeding state and after at least a 24-hour washout. Volume and units of factor infused must be calculated and recorded using the actual potency as described in Section 10.1.1 (and in the DHA). Predose sample is to be collected within 30 minutes before the start of the 50 IU/kg rFVIIIFc injection; postdose sample is to be taken 30 (±5) minutes after the start of the rFVIIIFc injection. IR assessments will be performed at the central laboratory.
[k] rFVIIIFc PK assessments for half-life determination are to be performed when the subject is in a non-bleeding state and after at least a 72-hour washout. See Section 4.2.2.4.
[l] The rFVIIIFc PK assessments for half-life will be performed at 12-week intervals, only after IR determinations of ≥66% of expected value on 2 consecutive months. The first rFVIIIFc PK assessment will occur 12 weeks after IR≥66% of expected value is confirmed; subsequent PK assessments will be performed every 12 weeks thereafter for subjects who have not yet achieved the criteria for ITI complete success.
[m] The subject's parent/caregiver must enter dosing information into the EPD ***as soon as possible after an injection and within a maximum of 7 days following the injection*** (Section 10.2.4.1.4). It is recommended that parents/caregivers enter dosing information immediately after an injection.
[n] Injection site inspection is only to be performed if the subject receives an rFVIIIFc injection during a clinic visit.
[o] For subjects who are receiving breast milk, maternal concomitant medications will also be collected at the same time points as other concomitant therapies, unless the breast milk is derived from a source other than the mother or the mother has not consented.

4.2.2.4. Schedule of Activities: Pharmacokinetic Sampling for Half-life Determination

Subjects with a confirmed negative inhibitor titer and confirmed IR ≥66% of expected who have not yet achieved the criteria for ITI complete success will undergo PK evaluation for $t_{½}$ every 12 weeks as described in Figure 2; monitoring for inhibitor and IR will continue on a monthly basis. Subjects must not have received an injection of rFVIIIFc within at least 72 hours of the predose sample collection. The PK dose will be 50 IU/kg of rFVIIIFc. Volume and units of factor infused must be calculated and recorded using the *actual* potency as described in the DHA (see Section 10.1.1).

The following Schedule of Activities applies only to subjects requiring PK assessments for determination of $t_{½}$ as described in Section 10.2.7.4.2, Section 10.2.7.4.3, and Section 10.2.7.6.

	Time in Relation to rFVIIIFc Dosing							
Activities	**Pre dose**[a]	**0**	**30 min (± 5 min)**	**3 hr (± 10 min)**	**6 hr (± 10 min)**	**24 hrs (± 60 min)**	**48 hrs (± 60 min)**	**72 hrs (± 2 hrs)**
rFVIII Dosing		X						
PK Assessments[b]	X		X	X	X	X	X	X

Hr=hours; min=minutes

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

[b] Timepoints for PK assessment are measured from start of the rFVIIIFc injection.

4.2.2.5. Schedule of Activities: Post-Immune Tolerance Complete Success Visits

The following Schedule of Activities applies only to subjects who meet the criteria for ITI complete success described in Section 10.2.7.4.2 and Section 10.2.7.5.

Activities	Tapering Period Visits Every 4 Weeks			Follow-up Monitoring for Relapse Visits Every 12 Weeks[a]		
	Month 1 (± 1 wk)	Month 2 (± 1 wk)	Month 3 (± 1 wk)	Month 6 (± 2 wks)	Month 9 (± 2 wks)	Month 12 (± 2 wks)
Physical Examination	X	X	X	X	X	X
Weight (kg)	X	X	X	X	X	X
Vital Signs[b]	X	X	X	X	X	X
Hematology[c]	X		X	X	X	X
Blood Chemistry[d]	X		X	X	X	X
Nijmegen-Modified Bethesda Assay (Inhibitor Assay)[e]	X	X	X	X	X	X
Blood Sample for Exploratory Biomarker Characterization[f]			X			
rFVIIIFc Dosing	X	X	X	X	X	X
FVIII Activity for Incremental Recovery[k]	X	X	X	X	X	X
FVIII Activity for Half-life Determination[g,h]						X
EPD Review, including rFVIIIFc Dosing Accountability[i]	X	X	X	X	X	X
Anti-rFVIIIFc Antibody	X	X	X	X	X	X
Injection Site Inspection[j]	X	X	X	X	X	X
Adverse Events[i]	<ONGOING; Monitor and record at all visits >					
Serious Adverse Events[i]	<ONGOING; Monitor and record at all visits >					
Concomitant Therapy/ Procedures Recording[i]	<ONGOING; Monitor and record at all visits >					

AE = adverse event; aPTT=activated partial thromboplastin; EOT = end of treatment; EPD=electronic patient diary; ET = early termination; FVIII = coagulation factor VIII; ITI = immune tolerance induction; rFVIIIFc = recombinant coagulation factor VIII Fc fusion protein; wk = week.

[a] The timing of the ET/EOT visit (Section 10.6) will vary for subjects fulfilling the criteria for ITI complete success, as described in Section 10.2.7.4.2. The minimum tapering period is 12 weeks. Subjects who develop inhibitors during the tapering phase (i.e., who relapse) will proceed immediately to the ET/EOT visit.

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

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

[d] 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.

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

[f] A whole blood sample will be drawn at the end of the tapering period, for exploratory assays related to immune response. Up to 10 mL of whole blood (minimum 3 mL) should be collected, as allowable based on patient weight and institutional practice regarding blood draw restrictions for pediatric patients.

[g] Volume and units of factor infused must be calculated and recorded using the *actual* potency as described in Section 10.1.1(and in the DHA).

[h] Half-life evaluation is performed under circumstances described in Section 10.2.7.4.3 , Figure 2, and Section 10.2.7.6. For the PK sampling schedule, see Section 4.2.2.4.

[i] Telephone call every month during the Follow-up Monitoring period.

[j] Injection site inspection is to be performed only if the subject receives an rFVIIIFc injection during a clinic visit.

[k] Blood samples will be taken at predose (within 30 minutes prior to the start of the rFVIIIFc injection) and postdose (30 ±5 minutes after the start of the rFVIIIFc injection).

4.2.2.6. Schedule of Activities: Surgery Visits

Activities	Pre-Surgery (Week -4 to Week -2)[a]	Preoperative Assessment/Day of Surgery[b]	Postoperative Visit (1 to 2 Weeks After Surgery)[c]	Last Postoperative Visit[d]
Physical Examination	X	X	X	
Weight (kg)	X	X	X	X
Vital Signs[e]		X	X	
Hematology[f]		X[g]	X	X
Blood Chemistry[h]		X[g]	X	X
FVIII Activity[i]	X[g]	X[g]	X	X
Nijmegen-Modified Bethesda Assay (Inhibitor Assay)	X[g]	X[g]	X	X
rFVIIIFc Clinic Dosing[j]	X	X	X	X
Anti-rFVIIIFc Antibody	X[g]	X[g]	X	X
EPD Review, including rFVIIIFc Dosing Accountability	X	X	X[k]	X
Investigator/Surgeon's Assessment of Response[l]		X	X	
AE/SAE Monitoring and Recording	X	X	X	X
Concomitant Therapy/Procedures Recording[m]	X	X	X	X

AE = adverse event; EOT = end of treatment; EPD = electronic patient diary; ET = early termination; FVIII = coagulation factor VIII; rFVIIIFc = recombinant coagulation factor VIII Fc fusion protein; SAE = serious adverse event.

[a] Not required for emergent surgery.

[b] If surgery is delayed by ≥8 weeks, preoperative assessments must be repeated. These include assessments of FVIII activity and Nijmegen-modified Bethesda assay. For minor surgery, the Investigator is to be in contact with the subject's parent/caregiver to determine when the subject should return to the regular prophylaxis regimen.

[c] Visit is required for major surgeries only.

[d] This visit is required for major surgeries only. This visit occurs when the Investigator determines that the subject can return to the regular pre-surgery regimen. This visit is not required if the return to the regular pre-surgery regimen occurs at the Postoperative Visit (1 to 2 weeks after surgery). If the subject is withdrawn from the study, then he will complete the ET/EOT Visit assessments (Section 4.2.2.1) at least 2 weeks after surgery.

[e] Vital signs include blood pressure, pulse rate, respiratory rate, and temperature (°C). Postdose assessments following in-clinic injections should be taken approximately 20 minutes after the end of the rFVIIIFc injection.

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

[g] For minor surgeries, this is only to be performed if indicated by the nature of the procedure, according to local standard of care.

[h] 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.

[i] Samples for the determination of predose FVIII activity levels will be collected prior to the dose of rFVIIIFc given for the surgery. FVIII activity levels will be sampled 30 (±5) minutes after the start of the rFVIIIFc injection. For major surgeries, a repeat blood draw for FVIII activity should be taken approximately 9 hours after the start of the injection but may alternatively follow local standard of care for determining when the next dose of rFVIIIFc should be administered. While hospitalized, blood will be drawn daily to be tested at the local laboratory for FVIII activity so that monitoring of the subject can occur in real time.

[j] Clinic dosing is applicable only if warranted.

[k] Subjects who require postoperative treatment with rFVIIIFc at home for a bleeding episode will have their assessment of response to treatment recorded in the EPD.

[l] For minor surgeries, assessment of response is conducted on the day of surgery. For major surgeries, assessment occurs 24 hours after surgery and at the Postoperative Visit (1 to 2 weeks after surgery). See Appendix D.

[m] For subjects who are receiving breast milk, maternal concomitant medications will also be collected at the same time points as other concomitant therapies, unless the breast milk is derived from a source other than the mother or the mother has not consented.

5. INTRODUCTION

In this study, previously untreated male subjects with severe hemophilia A will receive recombinant coagulation factor VIII Fc fusion protein (rFVIIIFc; BIIB031) according to local standard of care for implementation of a prophylaxis regimen, including an optional preceding episodic (on-demand) treatment regimen. The European Medicines Agency (EMA) Committee for Medicinal Products for Human Use (CHMP) guideline on the clinical investigation of recombinant and human plasma-derived factor VIII products [EMA (EMA/CHMP/BPWP/144533/2009) 2011] was followed in the development of this protocol.

5.1. Profile of Previous Experience

Hemophilia A is an X-linked bleeding disorder caused by mutations and/or deletions in the target gene for hemophilia A (F8) resulting in a deficiency of coagulation factor VIII (FVIII) activity [Bolton-Maggs and Pasi 2003; Mannucci and Tuddenham 2001]. Hemophilia A occurs predominantly in males and the worldwide incidence is approximately 1 case per 5000 male births. The severity of disease is characterized by the endogenous level of FVIII measured in the plasma. Severe hemophilia A is defined as a coagulation activity of FVIII in plasma (FVIII:C) of <1% (<1 IU/dL). Individuals with severe hemophilia A experience frequent bleeding and recurrent spontaneous bleeding into the soft tissue and joints, leading to joint damage and severe disability. Repeated bleeding into muscles and joints, which often begins in early childhood, results in hemophilic arthropathy and irreversible joint damage. Damage can lead to limited mobility of joints, muscle atrophy, and chronic pain [Rodriguez-Merchan 2003].

5.1.1. Therapies for Hemophilia A

There is no cure for hemophilia A, so treatment focuses on the replacement of FVIII with the intravenous (IV) administration of FVIII-containing coagulation products to promote clotting. The goal of treatment with FVIII-containing coagulation products is to raise the circulating level of FVIII to the lowest effective level to achieve either resolution of bleeding (on-demand treatment) or prevention of bleeding (prophylaxis treatment) [MASAC 2009; WFH 2005]. The frequency of administration of FVIII products varies across patients and is tailored to the patient's clinical status, taking into consideration the type of bleeding episode, frequency of bleeding, and goal of treatment for the patient. The dose of FVIII required also varies and has been based on observations over the years and guidelines established by organizations such as the National Hemophilia Foundation of the United States and the World Federation of Hemophilia [WFH 2005].

The use of FVIII-containing plasma-derived coagulation products for people with hemophilia A, available for almost 40 years has led to vast improvements in quality of life and has increased life expectancy. Manufacturing methods for plasma-derived products are now considered to be highly effective in reducing the risk of transmission of enveloped viruses such as human immunodeficiency virus (HIV) and hepatitis B and C viruses. However, these methods may not be effective in reducing the risk of non-enveloped viruses, such as hepatitis A and parvovirus

B19. Recombinant coagulation products developed more recently with no animal or human plasma-derived proteins have a safety advantage with a minimal risk of disease transmission [Mannucci and Tuddenham 2001].

Priorities for improving hemophilia A therapy include the development of more convenient dosing options and development of modified FVIII agents with a longer half-life ($t_{½}$) to decrease injection frequency. Current therapy is focused on home therapies, which, when taken prophylactically or administered at the onset of a bleeding episode, reduce short-term disability and long-term joint damage and improve patients' quality of life and functional independence [Colvin 2008].

5.1.2. rFVIIIFc

rFVIIIFc is a novel recombinant Fc fusion protein consisting of a single molecule of B-domain deleted FVIII attached to the Fc domain of human immunoglobulin G1. This type of construct has been termed a monomeric Fc fusion protein [Dumont 2006]. The Fc enables binding to the neonatal Fc receptor (FcRn), which is responsible for protecting immunoglobulin G (IgG) from degradation and confers IgG the 3-week $t_{½}$ observed in humans [Ghetie and Ward 2000; Roopenian and Akilesh 2007]. The FcRn is present in humans throughout life and protects IgG from catabolism [Junghans and Anderson 1996]. rFVIIIFc was designed to offer a longer circulating $t_{½}$ than currently available FVIII products, aiming to provide hemophilia A patients with prolonged protection and prophylaxis from bleeding with less frequent dosing.

5.1.3. Summary of Nonclinical Experience with rFVIIIFc

rFVIIIFc was evaluated in a comprehensive nonclinical program, which included pharmacokinetics (PK), pharmacology, and toxicology studies. The nonclinical program provided the following critical results:

- Improved PK parameters (e.g., increased elimination $t_{½}$) were observed for rFVIIIFc in several animal species, and administered rFVIIIFc retained its functional activity while present in the circulation.
- Prolonged pharmacodynamics and efficacy were observed for rFVIIIFc in 2 animal species deficient in FVIII.
- Similar potency was found for rFVIIIFc and recombinant FVIII (rFVIII) in an acute bleeding model.
- The toxicology program established that there were no adverse toxicological findings directly related to the effects of rFVIIIFc in 2 relevant species (rats and monkeys).
- The safety margin is 10-fold based on a comparison of no-observed-adverse-effect levels (1000 IU/kg) with the highest anticipated routine clinical dose of 100 IU/kg.

See the Investigator's Brochure for detailed information on nonclinical studies.

5.1.4. Summary of Clinical Experience With rFVIIIFc

Three clinical studies, including a Phase 1/2a study (Study 998HA101), a Phase 3 study in previously treated patients (PTPs) [Study 997HA301], and a Phase 3 pediatric study (Study 8HA02PED) have been completed. Ongoing clinical studies include an extension study (Study 8HA01EXT) and this PUPs study (Study 997HA306).

A completed Phase 1/2a study (Study 998HA101) investigated the safety of a single dose of rFVIIIFc given as an IV injection over 10 minutes to subjects with severe hemophilia A and compared the PK of rFVIIIFc with Advate® (Antihemophilic Factor [Recombinant], Plasma/Albumin-Free Method, [INN octocog alfa]). Inhibitor-positive subjects were excluded.

Two dose levels, 25 and 65 IU/kg, were evaluated, with 6 subjects receiving Advate 25 IU/kg, and 10 subjects receiving Advate 65 IU/kg. Following a 3-day PK profile for the Advate 25 IU/kg dose group and a 4-day PK profile for the Advate 65 IU/kg dose group, these subjects then crossed over to receive an equivalent dose of rFVIIIFc. A 7-day PK profile was performed after the 25 IU/kg dose. Following the rFVIIIFc 65 IU/kg dose, subjects underwent a 10-day PK profile. A 28-day safety observation period followed the rFVIIIFc dose and included inhibitor testing at 14 and 28 days post-dosing.

Safety and tolerability were assessed in all 16 subjects, including FVIII inhibitors and anti-FVIIIFc antibodies, vital signs, hematology, blood chemistry, and coagulation parameters.

When compared with Advate at both dose levels, rFVIIIFc was well tolerated. No clinically significant changes in safety parameters occurred, and most adverse events (AEs) were mild and resolved without sequelae by the end of the study. No subject developed antibodies or inhibitors during the study period. Compared with Advate, rFVIIIFc demonstrated a significantly longer $t_{½}$, an increased systemic exposure, and a reduction in clearance (CL) with comparable volume of distribution and recovery. The $t_{½}$ and mean residence time (MRT) of rFVIIIFc were both prolonged by 1.54-fold at 25 IU/kg and by 1.70- and 1.71-fold, respectively, at 65 IU/kg, relative to equivalent doses of Advate in this study.

Phase 3 Study 997HA301 was a study of previously treated subjects aged 12 years or older with severe hemophilia A, in which a total of 164 subjects (including 13 subjects aged 12 to 17 years) received at least 1 dose of rFVIIIFc. This included 146 subjects treated for at least 26 weeks and 23 subjects treated for at least 39 weeks, for a total of 102.05 person-years on study. Inhibitor-positive subjects were excluded.

Compared with Advate, rFVIIIFc demonstrated a 53% longer $t_{½}$, a 56% increase in systemic exposure, and a 36% reduction in CL, with comparable steady state volume of distribution and recovery (1-stage activated partial thromboplastin time [aPTT] clotting assay).

rFVIIIFc was generally well tolerated in the Phase 3 study. No subject developed an inhibitor to rFVIIIFc. Adverse drug reactions (ADRs) were defined as AEs assessed by the Investigator as related to the treatment with rFVIIIFc followed by medical review. The most common ADRs observed in the Phase 3 study (incidence >1%) were arthralgia and malaise. No serious adverse events (SAEs) were assessed as related to rFVIIIFc treatment by the Investigator. One

nonserious event of rash was assessed as related to rFVIIIFc, resulted in discontinuation of study treatment and resolved. There were no Grade 2 or greater allergic reactions or serious vascular thrombotic events. Overall, the AE profile was consistent with the background characteristics of the hemophilia A population.

Efficacy data from the Phase 3 study showed that rFVIIIFc was effective in the control and prevention of bleeding episodes and in perioperative management (surgical prophylaxis). For further details, see the rFVIIIFc Investigator's Brochure.

Study 8HA02PED (referred to as the pediatric study) was an open-label, multicenter study evaluating the safety, PK, and efficacy of rFVIIIFc in previously treated pediatric patients with severe hemophilia A, who were <12 years of age, and had at least 50 exposure days (EDs) to FVIII products prior to enrollment. The results from this study suggest that rFVIIIFc was well tolerated and effective for the control and prevention of bleeding when administered for routine prophylaxis using an individualized regimen. The pattern of treatment-emergent AEs reported during the study was typical of the population studied, and no unique safety issues were identified. No subject developed an inhibitor to rFVIIIFc. Efficacy data showed that rFVIIIFc was effective in the control and prevention of bleeding episodes and in perioperative management. A review of rFVIIIFc PK parameters by age group demonstrated an increase in the mean body-weight-normalized CL and a decrease in the mean $t_{½}$, MRT, and dose-normalized area under the curve (DNAUC) estimates for children <12 years of age compared to adults and adolescents ≥12 years of age (see Table 1).

Table 1: Comparison of PK Parameters of rFVIIIFc by Age Category: Geometric Mean (95% Confidence Interval)

	Pediatric Study (8HA02PED)		Phase 3 Study (997HA301)	
	<6 Years (N = 23)	**6 to <12 Years (N = 31)**	**12 to 17 Years (N = 11)**	**≥18 Years (N = 144)**
IR (IU/dL per IU/kg)	1.901 (1.785, 2.024)	2.299 (2.042, 2.587)	1.807 (1.561, 2.092)	1.925 (1.849, 2.004)
DNAUC (IU*h/dL per IU/kg)	28.93 (25.59, 32.72)	38.37 (33.20, 44.35)	38.15 (33.96, 42.87)	43.30 (40.82, 45.93)
$t_{½}$ (h)	12.28 (10.99, 13.72)	13.45 (11.45, 15.81)	16.04 (13.90, 18.53)	17.14 (16.37, 17.94)
MRT (h)	16.76 (15.11, 18.60)	19.00 (16.21, 22.26)	22.67 (19.67, 26.13)	24.37 (23.30, 25.49)
CL (mL/h/kg)	3.456 (3.056, 3.908)	2.607 (2.256, 3.012)	2.621 (2.333, 2.945)	2.310 (2.177, 2.450)
V_{ss} (mL/kg)	57.9 (54.1, 62.0)	49.5 (44.1, 55.6)	59.4 (52.7, 67.0)	56.3 (54.5, 58.2)

CL = clearance; DNAUC = dose-normalized area under the curve; IR= incremental recovery; MRT = mean residence time; PK = pharmacokinetic; rFVIIIFc = recombinant coagulation factor VIII Fc; $t_{½}$ = terminal half-life; V_{ss} = volume of distribution at steady state.

Study 8HA01EXT (referred to as the extension study) is an open-label, multicenter extension to both the Phase 3 study (Study 997HA301) and the pediatric study (Study 8HA02PED) as well as other studies in which subjects have received rFVIIIFc. The extension study is evaluating the long-term safety and efficacy of rFVIIIFc for prophylaxis and episodic treatment of bleeding episodes in previously treated patients with hemophilia A. The safety observations in the extension study are, so far, consistent with those from the Phase 3 study.

For further details regarding the clinical studies conducted with rFVIIIFc, and for descriptions of the potential risks and benefits of rFVIIIFc, see the rFVIIIFc Investigator's Brochure.

5.2. Study Rationale

The use of a prophylaxis regimen in young children starting prior to the onset of frequent joint bleeding is currently the recommended standard of care in hemophilia due to the demonstrated benefit on long-term outcomes [Aznar 2000; Manco-Johnson 2007; Molho 2000]. Currently available FVIII replacement therapies are limited by short elimination $t_{½}$.

The purpose of this study is to investigate the safety and efficacy of rFVIIIFc in previously untreated patients (PUPs) in accordance with the EMA CHMP guideline on the clinical investigation of recombinant and human plasma-derived factor VIII products [EMA (EMA/CHMP/BPWP/144533/2009) 2011].

5.3. Rationale for Dose and Schedule Selection

In the completed Phase 3 study (Study 997HA301), multiple doses of up to 65 IU/kg were well tolerated, with an AE profile generally consistent with that expected in patients with hemophilia A. Safety data from the completed pediatric study (Study 8HA02PED), which allowed for doses up to 80 IU/kg and a minimum dosing interval of 2 days, showed a safety profile consistent with the results of the Phase 3 study.

The dose for prophylaxis may be selected and adjusted based on the subject's response to dosing (i.e., available PK data, including FVIII activity levels, level of physical activity, and bleeding pattern), in the range of 25 to 65 IU/kg at 3 to 5 day intervals. However, based on data from the completed clinical studies, and knowledge of increased clearance of factor concentrates in children <6 years of age, more frequent or higher doses of up to 80 IU/kg may be required. Prophylactic dose titration outside the range of 25 to 80 IU/kg requires discussion with the Sponsor and documentation of rationale.

The dose for treatment of bleeding episodes will target peak plasma FVIII activity of approximately 40% to 100%, in accordance with local standards.

Subjects will be eligible to undergo immune tolerance induction (ITI) with rFVIIIFc if

- They develop a positive high titer inhibitor (≥5.00 Bethesda Units [BU]/mL), or

- They develop a positive low titer inhibitor (≥0.60 and <5.00 BU/mL) and experience poorly controlled bleeding despite increased rFVIIIFc doses, or require bypassing agents to treat bleeding.

The ITI regimen will approximate the high-dose treatment arm of the International ITI Study protocol [Hay and DiMichele 2012] and will utilize single injections of rFVIIIFc 200 IU/kg, daily, consistent with current ITI guidelines [Valentino 2015]. This dosing regimen is also supported by the results of a prospective clinical trial (the International ITI 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 and 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 to subjects treated with the low dose. Furthermore, subjects treated with the high dose for ITI had a lower rate of intercurrent bleeding and fewer hospitalizations due to bleeding than subjects treated with the low dose. 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 maximize the potential for rapid tolerization while minimizing bleeding-related adverse events.

If a subject requires surgery while participating in this study, the subject may be treated with the dose and regimen of rFVIIIFc deemed appropriate by the Investigator for the type of surgery. All major surgeries will be reported as serious adverse events (SAEs).

5.4. Potential Risks and Benefits

See the current Investigator's Brochure for descriptions of the potential risks and benefits of rFVIIIFc.

6. STUDY OBJECTIVES AND ENDPOINTS

6.1. Objectives

6.1.1. Primary Objective

The primary objective of the study is to evaluate the safety of rFVIIIFc in previously untreated subjects with severe hemophilia A.

6.1.2. Secondary Objectives

The secondary objectives of the study are as follows:

- To evaluate the efficacy of rFVIIIFc in the prevention and treatment of bleeding episodes in PUPs
- To evaluate rFVIIIFc consumption for the prevention and treatment of bleeding episodes in PUPs
- To describe experience with the use of rFVIIIFc for ITI in subjects with inhibitors

6.1.3. Exploratory Objective

The exploratory objectives are

- To evaluate the effect of rFVIIIFc based on patient-reported outcomes and health resource utilization
- To assess the efficacy of rFVIIIFc for perioperative management

6.2. Endpoints

6.2.1. Primary Endpoint

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

6.2.2. Secondary Endpoints

The secondary endpoints of the study are as follows:

- The annualized number of bleeding episodes per subject
- The annualized number of spontaneous joint bleeding episodes per subject

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

For additional information about the correspondence between the objectives and their associated endpoints and assessments, see Appendix E.

6.2.3. Exploratory Endpoints

The exploratory endpoints include, but are not limited to

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

7. STUDY DESIGN

7.1. Study Overview

This is an open-label, single-arm, multicenter study evaluating the safety and efficacy of rFVIIIFc in previously untreated pediatric subjects with severe hemophilia A when used according to local standard of care. Following the confirmation of eligibility, the Investigator has the option to treat eligible subjects episodically (on-demand) prior to initiating a prophylaxis regimen. The duration of episodic treatment is at the Investigator's discretion, in accordance with local standard of care. At least 90 previously untreated subjects are planned to complete the study after reaching at least 50 EDs with rFVIIIFc.

Baseline IR may be conducted along with other baseline assessments on the same day as screening, once the subject has been enrolled, or as part of a separate baseline IR visit, as long as the subject has not yet had more than 3 doses of rFVIIIFc.

Subjects with a documented plasma FVIII activity of <1% may be enrolled on the basis of local laboratory results and may receive study drug after samples for factor VIII activity level and inhibitors, for testing at the central laboratory, have been obtained. However, any such subject must be withdrawn if the central laboratory screening results indicate factor VIII activity level ≥1% or a positive inhibitor.

Major and minor surgery are allowed during the study (Section 10.2.8).

ITI with rFVIIIFc is allowed during the study for those subjects developing, after exposure to rFVIIIFc study drug, a positive high titer inhibitor (≥5.00 BU/mL) or a positive low titer inhibitor (≥0.60 and <5.00 BU/mL) with poorly controlled bleeding despite increased rFVIIIFc doses or requiring bypassing agents to treat bleeding (Section 10.2.5.2).

Because of the risk of allergic reactions with FVIII concentrates, the initial administrations of rFVIIIFc should be performed under medical observation where proper medical care for allergic reactions could be provided. The first injection of rFVIIIFc study drug after the Screening Visit must be administered by the Investigator or a qualified delegate. Thereafter, study treatment may be administered by a parent/caregiver or by a qualified medical professional under the direction of the Investigator. Study treatment may also be injected in the hospital during surgery or during hospitalization due to major bleeding.

See Figure 1 for a schematic of the study design. Section 4.2 provides schedules for the activities required for each study visit. Section 10 describes the treatment of subjects during the study.

7.2. Study Specifics

7.2.1. Dose-Limiting Toxicity

No dose-limiting toxicity (DLT) has been identified to date in humans receiving doses of rFVIIIFc up to 80 IU/kg. Also, no DLTs were observed in the nonclinical animal studies where repeated doses of up to 1000 IU/kg were evaluated. Single injections of rFVIIIFc up to 100 IU/kg are allowed [redacted] based on the individual subject's recovery and/or age-specific PK data for rFVIIIFc (see Table 1). Single, daily injections of rFVIIIFc 200 IU/kg will be allowed in the ITI regimen, since exposure is expected to be much lower in subjects undergoing ITI due to the presence of inhibitors.

7.3. Overall Study Duration and Follow-Up

The study period will consist of screening, treatment, and follow-up. Individual subject study participation is expected to be approximately 6 months to 3 years, including screening and follow-up. For subjects who do not develop an inhibitor, the treatment period is no less than 50 EDs to the study treatment.

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

See Figure 1 for a schematic of the study design.

7.3.1. Screening

Subject eligibility for the study will be determined within 8 weeks from the start of screening activities (Section 4.2.1, that is, all activities other than informed consent, which can occur prior to the subject's birth).

If more than 8 weeks elapse and screening activities have not been completed, the Nijmegen inhibitor and factor VIII antibody blood draws must be repeated. Other screening assessments that have not yet been completed must be completed within an additional 8 weeks

Potential subjects may be enrolled and receive study drug as long as they meet the minimum criteria for enrollment (Section 8.3). If the central lab factor VIII level is ≥1% or the central screening inhibitor test result is subsequently found to be positive, the subject must be withdrawn.

7.3.2. Treatment

Enrolled subjects will report to the study site for 2 kinds of required visits during the Treatment Period:

- Scheduled Interim Visits: every 12 (±2) weeks by calendar date (Section 4.2.2.1). Subjects who develop high titer inhibitors will switch to a schedule of ITI Induction

Visits (Section 4.2.2.3 and, if applicable, Section 4.2.2.4) and, if they subsequently meet ITI complete success criteria within 33 months, will receive a tapering regimen and participate in Post-ITI Success Visits (Section 4.2.2.5).

- ED Milestone Visits: at 5 (±1) EDs, 10 to 15 EDs, 20 to 25 EDs, and 50 to 55 EDs (Section 4.2.2.2).

In addition, telephone calls with the subject's parents/caregivers are planned approximately once a month. (Section 10.2.4.1.4).

Subjects who develop inhibitors may be eligible for 33 months of Immune Tolerance Induction Therapy (ITI), followed by a tapering off regimen of 3 months and follow up monitoring for 9 months (for a total of 12 months of monitoring post-ITI success) (Section 10.2.7, Section 4.2.2.4 and Section 4.2.2.5).

7.3.3. Follow-Up

Subjects are to return to the study site for the Early Termination/End of Treatment Visit (ET/EOT), followed by a final safety follow up visit or telephone call within 7 to 14 days following the ET/EOT Visit.

7.4. Study Stopping Rules

Bioverativ may terminate this study at any time, after informing Investigators. Investigators will be notified by Bioverativ or designee if the study is suspended, stopped, or closed.

Study stopping is required for the following:

- Unacceptable inhibitor incidence as determined by the Data Safety Monitoring Committee (DSMC; see Section 19.2)

- Detection of an unexpected, serious, or unacceptable risk to the study subjects

Data regarding frequency of inhibitor development will be reviewed by the DSMC at regular intervals. If, after consideration of subject-specific risk factors (e.g., genotype), the DSMC judges that the observed rate of inhibitor formation is unacceptable, compared with that reported for commercially available rFVIII concentrates, the study will be stopped.

If the study is stopped, the events will be investigated, enrollment will be stopped, and current subjects will stop dosing with rFVIIIFc. If, in consultation with the DSMC, it is determined that the study should be permanently discontinued, then subjects will attend a final visit.

7.5. End of Study

The end of the study (EOS) will occur after at least 90 subjects have reached at least 50 EDs with rFVIIIFc. Once this milestone has been achieved, all ongoing study subjects will return to the study center for the ET/EOT Visit assessments.

The end of treatment for individual subjects is described in Section 10.6.

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 screening, or at the time point specified in the individual eligibility criterion listed:

1. Ability of the subject's legally authorized representative (e.g., their parent or legal guardian) to understand the purpose and risks of the study and provide signed and dated informed consent and authorization to use confidential health information in accordance with national and local subject privacy regulations.

2. Male, age <6 years at the time of informed consent.

3. Weight ≥3.5 kg.

4. Severe hemophilia A defined as <1 IU/dL (<1%) endogenous FVIII documented in the medical record or as tested during the Screening Period. Any subject who is enrolled based on results of the local laboratory must be withdrawn if the central laboratory screening results indicate a baseline FVIII activity level ≥1% of normal.

8.2. Exclusion Criteria

Candidates will be excluded from study entry if any of the following exclusion criteria exist at screening or at the time point specified in the individual criterion listed:

1. Any exposure to blood components, factor VIII replacement products, including commercially available rFVIIIFc at any time prior to or during screening.

2. History of positive inhibitor testing. A prior history of inhibitors is defined based on a patient's historical positive inhibitor test using the local laboratory Bethesda value for a positive inhibitor test (that is, equal to or above lower level of detection).

5. History of hypersensitivity reactions associated with any rFVIIIFc administration.

6. Other coagulation disorder(s) in addition to hemophilia A.

7. Any concurrent clinically significant major disease that, in the opinion of the Investigator, would make the subject unsuitable for enrollment (e.g. HIV infection with CD4 lymphocyte count <200 µL or a viral load >200 particles/ µL, or any other known congenital or acquired immunodeficiency).

8. Current systemic treatment with chemotherapy and/or other immunosuppressant drugs. Use of corticosteroids for 1) the treatment of asthma or 2) management of acute allergic or otherwise life-threatening 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.

9. Participation within the past 30 days in any other clinical study involving investigational treatment.

10. Current enrollment in any other clinical study involving investigational treatment.

11. Inability to comply with study requirements.

12. Other unspecified reasons that, in the opinion of the Investigator or Bioverativ, make the subject unsuitable for enrollment.

8.3. Minimum Criteria for Enrollment

A subject may be enrolled as a subject when the following minimal criteria have been met:

- Diagnosis of severe hemophilia A with factor VIII <1% has been documented by local labs.
  - Laboratory data already present in the medical record are acceptable.
- Samples have been *drawn* for central laboratory testing for inhibitors and factor VIII activity.
  - The results are not required at the time of enrollment.
  - If central laboratory testing of the screening laboratory sample subsequently reveals a factor VIII activity level ≥1% or a positive inhibitor, the subject will discontinue treatment and be withdrawn per Section 11.
- The patient has met the remaining eligibility criteria described in the inclusion and exclusion criteria (Section 8.1 and Section 8.2) including the lack of exposure to blood components and factor VIII replacement products prior to enrollment.

9. ENROLLMENT AND REGISTRATION

9.1. Screening

9.1.1. Screening Assessments

The subject's legally authorized representative [e.g., parent or legal guardian], must be provided with the informed consent document(s) prior to the Screening Visit to allow adequate time for review and an opportunity to discuss the study with the Investigator/designee. After reviewing, parents/legal guardians will come into the clinic to sign the informed consent.

Parents/legal guardians of subjects must provide consent before any screening assessments are performed (see Section 17.3).

Subjects will be assigned a unique identification number as soon as informed consent has been obtained or at the Screening Visit. A centralized Interactive Web Response System (IXRS; see Section 19.1.2) will assign a unique 6-digit subject identification number to each subject. The unique number consists of the 3-digit site number (e.g., 105) and a sequential 3-digit subject number (e.g., 004). This number will be assigned regardless of whether the subject will be eligible for enrollment and subsequent treatment or not and will remain with the subject as the study-specific subject identifier. Any subject identification numbers that are assigned will not be reused even if the subject does not receive treatment. The study site is responsible for maintaining a current log of subject number assignments in order to avoid assignment errors, such as duplicating or skipping numbers. If a subject is excluded from the study, the reasons for exclusion will be documented in the subject's source documents and on the screening log. The subject's unique identification number must be entered on all study documentation (sample containers, drug accountability logs, source documents, etc.). As confirmation, the IXRS will provide the Investigator with written verification of the allocation of subject identification number by email or fax. See the Study Reference Manual for the IXRS User Manual.

Screening assessments should be completed within a total of 8 weeks from the start of the screening activities (not including informed consent, which can occur earlier) (Section 4.2.1). If more than 8 weeks have elapsed, and the subject has not been enrolled in the study, See Section 7.3.1. As part of the screening process, the Investigator must have sufficient documentation of a subject's medical history to ensure previously untreated status.

Subjects weighing <6 kg may require that blood draws for laboratory tests be collected over multiple days in order to comply with 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 (Section 14.4.3). Stored plasma samples (e.g., cord

blood, or blood obtained for diagnostic testing prior to the signature of the ICF) may be used at screening if:

- The samples were drawn within 28 days prior to the shipment day.
- The samples were collected and processed per the site's standard of care.
- The samples can be processed as specified in the Laboratory Manual.

Participating study sites are required to document all screened candidates initially considered for inclusion in this study. If a subject is excluded from the study, the reasons for exclusion will be documented in the subject's source documents and on the screening log.

9.2. Enrollment of Subjects

Subjects will be considered enrolled when the Investigator has verified that they are eligible according to the criteria in Sections 8.1 and 8.2 (see Section 9.1.1). Using the IXRS, the status of the subject should be updated to indicate the enrollment prior to dispensing study drug to the subject.

As confirmation, the IXRS will provide the Investigator with written verification of the subject's enrollment by email or fax.

After enrollment, the subject should be treated only with rFVIIIFc study treatment. Subjects treated with another FVIII concentrate must permanently discontinue study treatment and be withdrawn from the study, although exceptions are allowed for 1 emergency or accidental use.

9.3. Registration of Subjects

At the Screening Visit, an IXRS will be used to assign each subject a unique 6-digit subject identification number (see Section 9.1.1). See the Study Reference Manual for additional details about registration.

9.4. Blinding Procedures

Not applicable. This is an open-label study.

10. TREATMENT OF SUBJECTS

Bioverativ will provide rFVIIIFc to the study sites via its designated distributors.

10.1. Study Treatment Schedule and Administration

During the Treatment Period, subjects will be treated with rFVIIIFc according to schedules described in Section 4.2. See Figure 1 for a schematic of the study design and Section 7.3 for a description of the study duration.

Instructions for the preparation and administration of rFVIIIFc are provided in the Directions for Handling and Administration (DHA) and the Information for Patients. Dosing will be calculated as summarized in Section 10.1.1. See Section 12 for specifics on the preparation, storage, handling, disposal, and accountability of study treatment.

rFVIIIFc will be delivered via a slow push IV injection over several minutes, at a rate of administration determined by the subject's comfort level. Any missed doses should be taken as soon as possible or according to the instructions of the Investigator.

Because of the risk of allergic reactions with FVIII concentrates, the initial administration of rFVIIIFc should, according to the Investigator's judgment, be performed under medical observation, where proper medical care for allergic reactions could be provided. Parents/caregivers will be instructed to administer subsequent rFVIIIFc doses at home or to have it be administered by a qualified professional under the direction of the Investigator.

During the clinic visits and monthly telephone calls, the study site staff will verify whether or not a bleeding episode has occurred, and was "spontaneous" or "traumatic" (Section 10.2.4.1.4). During the monthly phone call, the subject's parent/caregiver will also be reminded about requirement that EPD data be entered as soon as possible, and within a maximum of 7 days following an injection.

Additional visits may be necessary during the study to test for inhibitors, test for recovery, repeat safety assessments, repeat any blood sampling if required for study purposes, or perform PK assessments if needed for surgical planning or adjustment of dosing regimen. Investigators are to report all inhibitor assessments performed throughout the study on the eCRF.

Subjects requiring surgery will also be followed via specialized visits (Section 4.2.2.6).

Treatment will continue until the subject has reached at least 50 EDs to rFVIIIFc, discontinues due to inhibitor development, completes ITI (with follow-up, if applicable), or the end of study is declared. The end of the study for all subjects is described in Section 7.5.

10.1.1. Definitions of Nominal Strength Versus Actual Potency

This section explains when the actual potency or nominal strength is to be used for dose calculations. The definitions of these terms and the types of dose calculations in this study are described below.

Definitions

- The *nominal strength* is the target potency of the vial (that is, 250 IU, 500 IU, 1000 IU, or 2000 IU per vial).
- The *actual potency* is the true potency of the vial as measured by a validated potency assay. (Actual potency may vary between 80 to 125% of nominal strength.)

Calculation and Recording of Actual versus Nominal Dosing

Actual potency must be used for dose calculations for the following:

- ***For partial vial use (Actual Potency dosing)***, **including the dose used for the calculation of Baseline IR, the dose used for IR and $t_{1/2}$ assessments during ITI,** and any other doses using partial vials. The ***actual*** potency shown on the vial must be used to calculate the units of rFVIIIFc and the volume to inject. Actual potency dosing is required for the dose of 25 IU/kg that is used to measure Baseline IR.

Note: The instructions and worksheets provided in the DHA manual must be used to calculate the *volume for administration based on actual potency* (unless an equivalent alternative site-specific template is approved by the responsible CRA prior to use). The actual potency shown on the vial must be used to calculate the volume for administration.

Nominal strength must be used for dose calculations for the following:

- ***Dosing for prophylactic treatment or treatment of bleeds,* as well as the dose used for FVIII activity at interim visits.** The ***nominal*** strength should be used for calculations. Whole vials should be used to achieve the target dose, rounded to the nearest 250 IU. These calculations should be discussed with the parent/caregiver during regular monthly phone calls.

Note: The instructions and worksheets provided in the DHA manual must be used to calculate the *number of vials for administration based on nominal strength* (unless an equivalent alternative site-specific template is approved by the responsible CRA prior to use).

10.2. Treatment

10.2.1. Incremental Recovery

10.2.1.1. Baseline Incremental Recovery Assessments

Baseline IR assessments described in Section 4.2.1 may be completed on the same day as Screening, or they may be completed as a part of a separate visit. Baseline IR requires a washout from rFVIIIFc of at least 24 hours prior to the predose sample collection.

For the Baseline IR measurement, a dose of 25 IU/kg will be given in clinic as an IV injection. The *actual* potency of rFVIIIFc must be used to calculate the units and volume of rFVIIIFc infused for the IR visit dose. (For additional details, see the DHA, as well as Section 10.1 of this protocol). rFVIIIFc will be delivered via a slow push IV injection over several minutes, at a rate of administration determined by the subject's comfort level.

Blood samples will be taken at trough (predose; within 30 minutes of the injection) and at 30 (±5) minutes after the start of the rFVIIIFc injection for the assessment of IR, and measured by the one-stage aPTT clotting assay and the chromogenic assay. The predose activity does not have to be collected if the subject has not received any dose of any product containing FVIII (including a blood transfusion) between screening and the dose for the baseline IR assessment.

10.2.1.2. Assessment of FVIII Activity During Interim Visits

If an injection is administered during an Interim Visit, predose and postdose samples will also be taken for dose adjustment purposes. The subject should be in a non-bleeding state.

The subject's current prophylactic dose of rFVIIIFc may be used for FVIII activity assessments at interim visits. *Nominal* strength should be used to calculate the units and volume of rFVIIIFc infused at Interim Visits. (For additional details, see the DHA, as well as Section 10.1.1 of this protocol).

rFVIIIFc will be delivered via a slow push IV injection over several minutes, at a rate of administration determined by the subject's comfort level.

Blood samples will be taken Predose (within 30 minutes prior to the start of the injection) and postdose (30 (±5) minutes after the start of the rFVIIIFc injection), measured by the one-stage aPTT clotting assay and the chromogenic assay. According to the local standard of care, an IV access device may be offered to facilitate sample collection. The IV access device must not be flushed with heparin between injection of rFVIIIFc and the collection of the samples.

Dosing for ITI IR is discussed separately in Section 10.2.7.1.

10.2.2. Episodic Treatment

The Investigator has the option to treat the subject episodically, starting after the confirmation of eligibility and lasting until a prophylactic regimen is initiated. Dosing will be determined by the

Investigator using the guidelines in Appendix A. The duration of episodic treatment is at the Investigator's discretion and should be based upon the Investigator's treatment plan for the subject in accordance with the local standard of care. However, given global standards of care, it is expected that the prophylactic regimen will be initiated prior to or immediately following a third episode of hemarthrosis [Berntorp 1995; Manco-Johnson 2007; MASAC 2007]. The date of transition from episodic treatment to a prophylaxis regimen must be captured on the electronic case report form (eCRF).

10.2.3. Prophylaxis Treatment

It is anticipated that subjects will begin a prophylaxis regimen prior to or immediately following the occurrence of a third hemarthrosis (joint bleed). The dose for initiation of prophylaxis may be chosen by the Investigator within the range of 25 to 80 IU/kg. However, based on data from the completed clinical studies, and knowledge of increased clearance of factor concentrates in children <6 years of age, more frequent or higher doses of up to 80 IU/kg may be required to minimize breakthrough bleeding events. The dose can be adjusted based on the subject's response to dosing in the range of 25 to 65 IU/kg at 3 to 5 day intervals. Adjustments to the dose and dosing interval can be made based upon available IR data, subsequent FVIII activity levels, level of physical activity, and bleeding pattern, in accordance with local standards of care for a prophylactic regimen.

Parents/caregivers will be instructed to administer rFVIIIFc at home or to have it be administered by a qualified professional under the direction of the Investigator. Treatment will continue until the subject has reached at least 50 EDs to rFVIIIFc study drug, completed follow up of an ITI regimen, or the end of study is declared, see Section 7.5).

10.2.4. Bleeding Episodes

10.2.4.1.1. Definition of a Bleeding Episode

In this study, a bleeding episode will be defined as follows: A bleeding episode starts from the first sign of a bleed and ends no more than 72 hours after the last injection to treat the bleed, within which any symptoms of bleeding at the same location, injections less than or equal to 72 hours apart, are considered the same bleeding episode. Any injection 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.

In this study, when a subject reports a bleeding episode or hemorrhage and is treated with study drug, it will be classified as 1 of 2 types: spontaneous or traumatic. The subject's electronic patient diary (EPD) will serve as the source document for bleeding episodes while on study.

Spontaneous bleeding episodes: Bleeding episodes should be classified as spontaneous if a parent/caregiver records a bleeding event when there is no known contributing factor such as a definite trauma or antecedent "strenuous" activity. The determination of "strenuous" is at the

discretion of the Investigator, and the parent/caregiver/subject needs to be instructed by the Investigator.

Traumatic bleeding episodes: Bleeding episodes should be classified as traumatic if the parent/caregiver records a bleeding episode even when there is a known or believed reason for the bleed. For example, if a subject were to exercise strenuously and then have a bleeding episode in the absence of any obvious injury, the bleeding episode would still be recorded as traumatic. Target joint bleeding episodes can be traumatic if a known action led to bleeding into the joint. The Investigator should consider whether events resulting in a traumatic bleeding episode qualify as AEs and should be reported as such.

10.2.4.1.2. Procedure to Treat the Bleeding Episode

After meeting eligibility criteria, all bleeding episodes should be treated with study drug, either as part of an episodic treatment regimen or on an as-needed basis on the background of prophylactic treatment. Dosing calculations should be performed as described in the DHA and as summarized in Section 10.1.1, with respect to the use of nominal strength for the administration of whole vials and actual potency for the administration of partial vials.

The subject's parents/caregivers should be instructed to treat at the first sign of a bleeding episode and with a single dose of rFVIIIFc. Most bleeding episodes should resolve with a single dose of rFVIIIFc.

The dose of rFVIIIFc to treat the bleeding episode will be based on the subject's clinical condition, known PK information (including Table 1), type and severity of the bleeding event (see Appendix A for guidance on dosing), and input from the Medical Monitor, if necessary.

- If the bleeding episode resolves with a single IV dose of rFVIIIFc, the subject will return to the schedule of dosing used prior to the bleeding episode.

- If the bleeding episode does not resolve within 24 hours with the single IV dose of rFVIIIFc, the subject's parents/caregivers should contact the Investigator for advice. Administration of a second dose of rFVIIIFc as follow-up treatment will be determined by the Investigator based on the subject's clinical condition. Once the bleeding event resolves, the subject will return to the rFVIIIFc dosing schedule used prior to the bleeding episode.

- If the bleeding episode does not resolve with 2 doses (initial and follow-up treatments) of rFVIIIFc, the subject's parents/caregivers should contact the Investigator for advice. A third dose of rFVIIIFc will be administered within 24 hours after the administration of the second dose of rFVIIIFc. The repeat dose may be at the same dose or a dose determined by the Investigator based on the subject's clinical condition. Once the bleeding event resolves, the subject will return to the rFVIIIFc dosing schedule used prior to the bleeding episode.

- If the bleeding event has still not resolved with 3 doses (initial and 2 follow-up treatments) of rFVIIIFc, the Investigator should consult with the Medical Monitor to determine if the subject should be withdrawn from the study (see Section 11).

10.2.4.1.3. Dose and/or Interval Modification Following Bleeding Episodes

See Section 10.2.4.1.2 for guidance on dose and/or interval modification.

10.2.4.1.4. Information to be Recorded

The incidence of bleeding in this study will be obtained from EPDs, eCRFs, and medical records. Information on dosing and bleeding episodes treated with rFVIIIFc study drug prior to the subject being issued with an EPD upon confirmation of eligibility (Section 8.3) should be recorded in the eCRF (including date and location of bleed, type of bleeding episode, dose, date of injection, and response to treatment).

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

All injections administered during a study site visit must be recorded in the eCRF. An injection administered during a clinic visit must not be recorded in the EPD. Injections cannot be logged in both places. All injections performed while the subject is in the hospital for surgery must be recorded in the eCRF.

The subject's parent/caregiver must enter dosing information into the EPD ***as soon as possible after an injection and within a maximum of 7 days following the injection,*** to ensure data integrity, and to facilitate appropriate medical review and dosing guidance. It is recommended that parents/caregivers enter dosing information immediately after an injection.

The clinical sites and Clinical Monitors will ensure that there is consistency between the subject's medical record, IXRS, source documents, EPD, and eCRFs. During the clinic visits and monthly telephone calls with the subject's parents/caregivers, the Investigator will verify whether or not a bleeding episode has occurred and was "spontaneous" or "traumatic." The subject's parent/caregiver will also be reminded about timely EPD completion during the monthly phone call.

If, following this discussion, the Investigator judges that the classification by the subject's parents/caregivers was incorrect, the Investigator will document it in the subject's medical records with the rationale for the new classification, and the eCRF, documenting the new classification of the bleeding episode according to the Investigator and whether or not the subject's parents/caregivers agreed with this new classification. With regard to dose changes, the Investigator's classification of spontaneous or traumatic will be used (if different from the classification recorded in the EPD by the parent/caregiver). Both spontaneous and traumatic bleeding episodes will be collected.

Information collected in the EPD will include, but not be limited to, the following:

- The type of bleeding episode (that is, spontaneous or traumatic) and if related to sports activity or physical activity
- The date the bleeding event occurred
- The dose administered to treat the bleeding episode including any repeat doses
- The location of the bleed
- The reason for administering the dose (medical or nonmedical reasons [e.g., training for administration of study treatment])
- The caregiver's rating of treatment response

10.2.5. Inhibitor Testing

Subjects must be tested for the formation of inhibitors to rFVIIIFc under the following circumstances:

- At each clinic visit (Section 4.2.2.1). If for some reason, the inhibitor test could not be performed on the scheduled visit, an additional visit should be schedule to perform the test.
- At specific ED milestones (Section 4.2.2.2). Inhibitor testing at these ED milestones may be combined with scheduled study visits. However, if they do not align with a scheduled study visit, an additional visit must be scheduled to complete this testing.
- If required by the local standard of care or at the Investigator's discretion. Additional unscheduled testing may be performed under these circumstances.
- If inhibitor development is suspected at any time during the study (e.g., the expected plasma FVIII activity levels are not attained or if bleeding is not controlled with an expected dose). The subject will be tested for inhibitors by the central laboratory.
- Perioperatively (Section 4.2.2.6). For minor surgeries, testing for inhibitors will only be performed if indicated by the nature of the procedure, according to local standard of care.
- At ITI visits (Section 4.2.2.3) and Post-ITI Complete Success Visits (Section 4.2.2.5)
- At the ET/EOT Visit (Section 4.2.2.1). A valid inhibitor test result is required from the ET/EOT Visit. If the ET/EOT Visit inhibitor test is not evaluable, or if a sample is needed to obtain a sample to confirm a positive inhibitor test result, an unscheduled visit may be required to repeat inhibitor testing under this protocol

The results will be recorded on the eCRF.

10.2.5.1. Definition of Negative and Positive Inhibitors

10.2.5.1.1. Negative Inhibitor

A negative inhibitor is defined as an inhibitor test with a result of <0.6 BU/mL.

10.2.5.1.2. Positive Inhibitor

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

- A positive low titer inhibitor is defined as an inhibitor test with a result of ≥0.60 and <5.00 BU/mL.
- A positive high titer inhibitor is defined as ≥5.00 BU/mL.

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

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

10.2.5.2. Positive Inhibitors

Subjects developing positive inhibitors will be further classified as having low or high titer inhibitors and followed as described below. Subjects with confirmed or suspected inhibitors may receive bypassing agents. For more information on the use of bypassing agents see Section 10.2.5.2.3.

10.2.5.2.1. Low Titer Inhibitors

At the discretion of the Investigator, subjects developing positive low titer inhibitors (≥0.60 and <5.00 BU/mL) may continue on study at the same or higher dose per injection of rFVIIIFc. These subjects will continue with the schedule of assessments in Section 4.2.2.1 .

The subject will be eligible for ITI if the Investigator determines that bleeding is no longer adequately controlled despite increased rFVIIIFc doses or if bypassing agents are required to treat bleeding in a subject with a positive low titer inhibitor (see Section 5.3). Subjects undergoing an ITI regimen will follow the schedule of assessments in Section 4.2.2.3. If the subject declines to undergo or continue ITI, he will be withdrawn from the study.

10.2.5.2.2. High Titer Inhibitors

Subjects developing positive high titer inhibitors (≥5.00 BU/mL) will be eligible for ITI (see Section 10.2.7). Subjects undergoing an ITI regimen will follow the schedule of assessments in Section 4.2.2.3. If the subject declines to undergo or continue ITI, he will be withdrawn from the study.

10.2.5.2.3. Use of Bypassing Agents

Subjects with confirmed or suspected inhibitors may receive bypassing agents (aPCC [FEIBA] or rFVIIa [NovoSeven]) at the discretion of the Investigator and within labeled dosing recommendations for the specific bypassing agent. The Investigator may prescribe bypassing agents for active bleeding or 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.

In subjects with low-titer inhibitors, bleeding events may be controlled with increased doses of replacement FVIII to overwhelm the inhibitor by antigen excess. In subjects with high-titer inhibitors, bleeding may be treated with bypassing agents, which can bypass FVIII inhibition. During the study, the Investigator will determine if increased doses of replacement FVIII or use of bypassing agents is appropriate.

During ITI treatment, subjects may also receive bypassing agents as needed for active bleeding or if there is a high clinical suspicion of bleeding or potential for bleeding. The use of bypassing agents in the setting of ITI requires awareness of FVIII activity levels and close monitoring for cessation of bleeding events.

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 must be communicated to the Sponsor Medical Monitor with documentation of rationale.

All use of bypassing agents must be documented in the appropriate section of the eCRF.

10.2.6. Anti-rFVIIIFc Antibody Testing

Blood samples will be collected for anti-rFVIIIFc antibody [redacted] testing according to the Schedules of Activities (Section 4.2). Samples may also be collected and archived at the time of any clinical event deemed relevant to rFVIIIFc antibody testing. [redacted]

10.2.7. Immune Tolerance Induction Therapy

Subjects who develop high titer inhibitors as defined in Section 10.2.5.2.2 and choose to remain in the study will undergo ITI with rFVIIIFc, as described below. Subjects with low titer inhibitors as defined in Section 10.2.5.2.1 will be eligible for ITI if the Investigator determines that bleeding is no longer adequately controlled despite increased rFVIIIFc doses or if bypassing agents are required to treat bleeding in a subject with a positive low titer inhibitor (see Section 5.3). Separate consent is required before starting an ITI regimen.

The timing of ITI initiation in patients with a peak inhibitor titer of >10 BU/mL, including patients who experience serious or life-threatening bleeding or have frequent mild to moderate bleeding, will be based on the Investigator's clinical judgement.

If an investigator chooses to have the subject temporarily suspend treatment with rFVIIIFc, and delay the start of ITI, the subject should continue to participate in Interim visits every 12 ± 2 weeks (per the prophylaxis schedule in Section 4.2.2.1).

The ITI regimen will approximate the high-dose treatment arm of the International ITI Study protocol [Hay and DiMichele 2012] and will utilize single injections of rFVIIIFc 200 IU/kg, daily. Concomitant immunomodulation will not be allowed during ITI therapy.

ITI outcomes will be assessed on an ongoing basis as described in Section 10.2.7.4. Additional informed consent must be obtained prior to the ITI assessments beginning at Day 0.

Immune tolerance induction therapy assessments will be performed according to the schedule as described in Section 4.2.2.3.

10.2.7.1. Assessment of Incremental Recovery and Half-Life During Immune Tolerance Induction Therapy

Upon the confirmation of a negative inhibitor titer, IR and $t_{½}$ will be performed per the schedule of assessments (Section 4.2.2.3). Doses given for the purposes of full PK measurements (that is, $t_{½}$), and IR will be calculated and recorded using the *actual* potency written on the vial as described in Section 10.1.1. IR and $t_{½}$ assessments will be based on the one-stage clotting assay. The IR and $t_{1/2}$ will be calculated by the Sponsor and provided to the PI.

For PK assessments, the subject must not be currently bleeding:

- Blood samples for recovery assessments will be taken predose (within 30 minutes prior to the start of the injection) and at 30 (±5) minutes after the start of a 50 IU/kg injection of rFVIIIFc. Subjects are required to have at least a 24-hour washout prior to the predose sample collection.

- For PK assessments to determine $t_{½}$, subjects must not have received an injection of rFVIIIFc within at least 72 hours of the predose sample collection. Sampling will occur at the following time points: predose and 30 (±5) minutes; 3 and 6 hours (±10 minutes); and 24 hours (±60 minutes), 48 hours (±60 minutes), and 72 hours

(±2 hours) after a 50 IU/kg injection of rFVIIIFc. Subjects should not have any additional doses of rFVIIIFc during the PK sampling period. If additional doses are required for clinical care, please immediately inform the Sponsor, as the $t_{1/2}$ assessments must be repeated.

Whole blood will be drawn for exploratory assays related to immune response during ITI, starting with a sample collected at the pre-ITI assessment visit. A whole blood sample will be drawn every other month during ITI, at the time of the confirmation of complete success, partial success, or failure, and at the end of tapering (if applicable). Up to 10 mL of whole blood (minimum 3 mL) should be collected, as allowable by patient weight and institutional practice regarding blood draw restrictions for pediatric patients.

10.2.7.2. Treatment of Bleeding Episodes During Immune Tolerance Induction Therapy

At the Investigator's discretion, activated prothrombin complex concentrates, recombinant activated coagulation factor VII, and rFVIIIFc can be used to treat active bleeding or to provide surgical hemostasis during ITI.

10.2.7.3. Interruption of Immune Tolerance Induction Therapy

Interruptions of ITI should be avoided wherever possible and not exceed a maximum of 2 weeks. Subjects who discontinue ITI after less than 33 months will be withdrawn from study, unless they have already met the criteria for successful immune tolerance described in Section 10.2.7.4 .

10.2.7.4. Immune Tolerance Induction Therapy Outcomes

The outcome of ITI (complete success, partial success, or failure) will be assessed in the study via the algorithm provided in Figure 2. Potential outcomes are defined below.

10.2.7.4.1. Reference Incremental Recovery Values for ITI

The reference IR Value (expected recovery), which is the basis for one of the criteria for complete ITI success, is defined below:

- For subjects who have a baseline IR value, ≥66% of the subject's baseline value (if the subject's baseline IR value was obtained via the Baseline IR visit), OR
- [redacted]

10.2.7.4.2. Definitions of Complete Success, Partial Success, and Failure of Immune Tolerance Induction Therapy

Complete Success:

Complete ITI success requires that all of the following criteria be met:

1. Negative inhibitor titers in 2 consecutive determinations at least 1 month apart

13. IR ≥66% of expected in 2 consecutive determinations at least 1 month apart

14. $t_{½}$ ≥6 hours

Subjects may meet the criteria for complete success in less than 33 months.

Subjects fulfilling the criteria for complete success will transition to a "tapering" regimen over a minimum period of 12 weeks with the aim of starting a prophylactic rFVIIIFc regimen, as described in Section 10.2.7.5, and will be monitored for relapse for up to 9 months as described in Section 4.2.2.5.

Partial Success:

The determination of partial success will be made only for subjects who have completed 33 months of ITI but who do not fulfill the criteria for complete success.

To achieve partial success, the following criteria must be met after subjects have completed 33 months of ITI:

1. Negative inhibitor titers on 2 consecutive tests within 2 months of each other

   AND

15. Either of the following but not both:

    - IR ≥66% of expected

      OR

    - $t_{½}$ ≥6 hours

If the subject has 2 negative inhibitor tests but recovery is <66% of the subject's baseline value (if known) [redacted], then the subject may remain on ITI at the discretion of the Investigator, up to a total duration of ITI of 33 months.

Failure:

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

10.2.7.4.3. Algorithm for Determining the Outcome of Immune Tolerance Induction

Assessments to be performed during the ITI regimen are described in Section 10.2.7.4. Additional assessments may be required, per Figure 2 below and the Schedule of Assessments in Section 4.2.2.3.

If subjects begin the ITI regimen but discontinue the regimen without meeting the criteria for successful immune tolerance, they will be withdrawn from the study. (See Section 11)

Figure 2: Immune Tolerance Induction Assessment Algorithm

[a]See Section 4.2.2.3 for complete Schedule of Activities for ITI.
[b]See Section 10.2.5 for definitions of a positive low and high titer inhibitors.
[c]See Section 10.2.7.4.1 for the definition of expected values, and Section 10.2.7.4.2 for ITI success criteria.
[d]See Section 4.2.2.4 for Schedule of Activities for Half-Life Determination
[e]See Section 4.2.2.5 for Schedule of Activities for Tapering Regimen.

10.2.7.5. Transition to a Prophylactic Regimen Following Immune Tolerance Induction Therapy Success (Tapering Period)

Subjects fulfilling the criteria for complete ITI success will transition ("taper off") to a prophylactic regimen over a minimum period of 3 months. The duration of the tapering period

may be modified by the Investigator with the Sponsor's medical monitor's approval based on the subject's clinical response.

The suggested "tapering" schedule is similar to that used on the International ITI Study protocol [Hay and DiMichele 2012]:

[redacted]

Prophylaxis Regimen during Follow-up: Based on clinical response, adjust the prophylaxis regimen in the range of 25 to 65 IU/kg every 3 to 5 days, utilizing more frequent dosing or doses up to 80 IU/kg, as required.

10.2.7.6. Monitoring for Relapse

During the 9-month period following the end of the tapering off (Section 10.2.7.5), the subjects will be monitored for relapse via blood samples processed by the central laboratory using the Nijmegen-modified Bethesda assay for inhibitor detection, as well as IR assessments. The inhibitor titer and IR will be measured every 3 months for the follow up period. rFVIIIFc half-life assessments will be performed 12 months after ITI success.

If any of these tests indicate the possibility of an inhibitor at any time between the start of tapering through the beginning of prophylaxis, the tests must be repeated within 2 to 4 weeks to confirm relapse.

Relapse is defined as any of the following, occurring within 12 months following complete ITI success, based on the International ITI criteria [Hay and DiMichele 2012]:

- A positive inhibitor (≥0.6 BU/mL using the Nijmegen assay) that is confirmed by a second test result of ≥0.60 BU/mL from a separate sample, drawn approximately 2 to 4 weeks following the date when the original sample was drawn.
- [redacted]
- $t_{½}$ <6 hours.

10.2.8. Surgery

For subjects who require emergent or elective surgery during the study period, the target FVIII levels for the proposed procedure will be those deemed appropriate by the Investigator for the

type of surgery to be performed. Recommendations for the appropriate dosing regimen of rFVIIIFc during the surgery may be discussed between the Investigator and the Medical Monitor taking factors such as standard doses of FVIII for the type of surgery, the clinical status of the subject, and IR data for the subject into consideration.

All doses administered in the hospital will be captured in the eCRF. The subject's parent/caregiver should not enter these doses in the EPD.

See Section 4.2.2.6 for the surgery visit schedule.

10.2.8.1. Definitions of Major and Minor Surgery

Surgeries, elective or emergent, will be classified as major and minor as follows:

- Major surgery is defined as any surgical procedure in which a major body cavity is penetrated and exposed or for which a substantial impairment of physical or physiological function is produced (e.g., laparotomy, thoracotomy, craniotomy, joint replacement, or limb amputation).

- Minor surgery is defined as any surgical procedure that does not qualify as major (e.g., minor dental extractions, incision and drainage of abscess, port placement, or simple excisions).

10.2.8.2. Definition of the Surgical Period

The surgical period includes Preoperative, Intraoperative, and Postoperative Periods:

- The preoperative period of the study (that is, the beginning of the surgical period) begins with the first dose of rFVIIIFc given for the surgery. For elective surgeries, this is the pre-surgery dose.

- The intraoperative period is defined as the time from when the surgery begins to the time when the surgery is completed.

- The postoperative period is defined as the time period following the end of surgery through the last dose of rFVIIIFc given for the surgery, as judged by the Investigator/Surgeon, including doses given to prevent bleeding during the postoperative period.

10.2.8.2.1. Minor Surgery

Minor surgery is allowed at any time during the study.

For minor surgeries, pre-surgery assessments of FVIII trough and recovery, inhibitor, and anti-rFVIIIFc antibody, and hematology and blood chemistry on the day of surgery are only to be performed if indicated by the nature of the procedure, according to local standard of care.

If FVIII activity levels and inhibitor formation assessments are indicated, predose samples will be collected prior to the dose of rFVIIIFc given for the surgery, and FVIII recovery levels will be sampled 30 (±5) minutes after the start of the rFVIIIFc injection.

Bleeding caused directly by surgery should not be reported, although undesired or unexpected bleeding during or after surgery should be recorded on the eCRF. The Investigator or Surgeon's assessment of response will be conducted on the day of surgery.

The Investigator will contact the subject's parent/caregiver after the day of surgery to determine when the subject returns to his regular dosage regimen.

10.2.8.2.2. Major Surgery

Major surgery will only be allowed in the study after the subject has had at least 3 injections of rFVIIIFc without safety concerns. If a subject needs to undergo major surgery prior to 3 injections, they will be withdrawn from the study. The Investigator must consult with Bioverativ in advance of the surgery.

All major surgeries must take place in a center that can provide study treatment, trained study personnel, postoperative assessments, and hematological consult by the Investigator or Sub-Investigator. If surgery does not take place in such a setting, the subject will be withdrawn from the study.

In addition, subjects who require major surgery may receive rFVIIIFc if:

1. The surgery occurs within the contracted institution for the study and/or a separate agreement has been executed, permitting the use of study drug and Bioverativ's rights to data generated in the study at an alternative institution deemed appropriate by the Principal Investigator or designee.

2. The Investigator and/or appropriate qualified/licensed delegate is available to:
    a. Administer all rFVIIIFc doses required during surgery and during postoperative rehabilitation (if applicable).
    b. Provide medical oversight and guidance throughout the duration of the preoperative and the intraoperative periods.

All major surgeries will be reported as SAEs, even if the surgery does not otherwise meet the definition of an SAE.

Samples for determination of predose FVIII activity levels and inhibitor formation will be collected prior to the dose of rFVIIIFc given for the surgery, and FVIII recovery levels will be sampled 30 (±5) minutes after the start of the rFVIIIFc injection.

For major surgeries, a repeat blood draw for FVIII activity should be taken approximately 9 hours after the start of the injection, but may alternatively follow local standard of care for determining when the next dose of rFVIIIFc should be administered. While hospitalized, blood

will be drawn daily to be tested at the local laboratory for FVIII activity so that monitoring of the subject can occur in real time.

Bleeding caused directly by surgery should not be reported, although undesired or unexpected bleeding during or after surgery should be recorded on the eCRF. The Investigator or Surgeon's assessment of response is conducted 24 hours after surgery and at the Postoperative Visit (1 to 2 weeks after surgery).

A postoperative visit will be required following major surgery.

10.2.8.3. Rehabilitation Period

If surgery-related dosing is to be continued during postoperative rehabilitation, the dose of rFVIIIFc will be adjusted to achieve a trough at a sufficient level to maintain hemostasis, including during physical therapy. These doses will be captured in the subject's EPD.

Subjects will return to their pre-surgery regimen once all dosing for the postoperative period has been completed.

10.3. Treatment Precautions

Medications and resuscitation equipment for the emergency management of anaphylactic reactions must be available where the subject's first injection of rFVIIIFc is being performed. The subject's first injection must be performed by the Investigator or by qualified medical personnel identified by the Investigator. In addition, the parents/caregivers will be provided with specific instructions by the Investigator on what to do should such an event occur while at home, including how to seek emergency medical treatment.

10.4. Modification of Dose and/or Treatment Schedule

Information on modifications to the dose and treatment schedule can be found in Section 10.2.4.1.2.

10.5. Non-Medical Treatment With rFVIIIFc

During the study, subjects' parents/caregivers may attend training sessions on administration of rFVIIIFc. Administration of rFVIIIFc to subjects for training purposes will be considered non-medical treatment. Such training is permitted and must be recorded in the EPD. However, administration of the first dose of rFVIIIFc must be performed under supervision in the clinic. Data from this time period will be excluded from the analysis of consumption.

10.6. End of Treatment

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

- Any individual subject who completes at least 50 EDs of rFVIIIFc and is not on an ITI regimen is considered to have completed treatment.

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

  – The subject has achieved complete ITI success (as defined in Section 10.2.7.4) and has completed the tapering and monitoring periods described in Section 10.2.7.5 and Section 4.2.2.5.

  – The subject has completed 33 months on an ITI regimen without achieving complete ITI success (that is, ITI failure or partial ITI success) [Section 10.2.7.4, Figure 2].

Individual subjects may also have to end treatment because 1 of the following has occurred:

1. The subject has met criteria for early withdrawal (Section 11).

2. Study stopping rules have been met (Section 7.4).

3. EOS has been reached (Section 7.5).

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

The Final Safety Follow-up Visit (by telephone or in person) will be conducted within 7 to 14 days after the last dose of rFVIIIFc to assess the subject's status, collect AEs and/or SAEs and concomitant medications and procedures and follow up on open AEs and SAEs. (Section 4.2.2.1)

10.7. Treatment Compliance

Compliance with treatment dosing is to be monitored and recorded by site staff. The instructions provided in the DHA must be followed, as summarized in 10.1.1.

For the doses that will be administered at the study site, the study treatment will be administered under controlled conditions by the investigational staff; therefore, full compliance with study treatment is anticipated.

For between-visit administration, subjects' parents/caregivers or a qualified medical professional under the direction of the Investigator will administer rFVIIIFc and will record treatment in the EPD. The EPD will be reviewed during periodic calls to the subject's parents/caregiver and at each clinic visit.

10.8. Concomitant Therapy and Procedures

The use of concomitant therapies or procedures defined below must be recorded on the subject's eCRF according to instructions for eCRF completion. AEs related to administration of these therapies or procedures must be documented on the appropriate eCRF.

10.8.1. 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/Telephone Call. For subjects who are receiving breast milk, the mother will provide consent to collect the concomitant medications that she is taking (as part of the main parental consent). The mother's concomitant medications will not be collected if the breast milk is derived from a source other than the mother, if the mother will not consent, or if the mother is no longer breastfeeding. The list of disallowed concomitant medications in Section 10.8.1.2 does not apply to the mother's medications.

The subject's parents/caregivers should be instructed that the child not start taking any new medications, including nonprescription drugs and herbal preparations, unless they have received permission from the Investigator.

10.8.1.1. 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], rFVIIa [NovoSeven]) are allowed in subjects with confirmed or suspected inhibitors as outlined in Section 10.2.5.2. All such therapy must be recorded in the eCRF. The prophylactic use of bypassing agents in subjects with confirmed or suspected inhibitors must be communicated to the Sponsor Medical Monitor with documentation of rationale.

10.8.1.2. Disallowed Concomitant Therapy

No other drug under investigation may be used concomitantly with the study treatment. Subjects are not allowed to participate concurrently in another 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 ITI therapy.
- Emicizumab (Hemlibra)

- Any other FVIII product (exception allowed for 1 emergency or accidental use).

10.8.2. Concomitant 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.

10.9. Continuation of Treatment

No further provisions are made for access to the study treatment. If rFVIIIFc is proven to be beneficial, all regulatory requirements regarding post study access will be met.

11. WITHDRAWAL OF SUBJECTS FROM THE STUDY

A subject *must* permanently discontinue study treatment and be withdrawn from the study if any of the following occur:

1. The subject is found to have a factor VIII activity ≥1% or a positive inhibitor based on central laboratory results obtained during the screening period.

2. The subject develops a positive inhibitor following enrollment and is eligible for ITI (as defined in Section 10.2.5.1) AND opts not to undergo or continue ITI.

3. A subject who is in the tapering period (or the subsequent follow-up monitoring period) develops inhibitors (that is, has a relapse) (Section 4.2.2.5).

4. The subject develops a Grade 2 or greater allergic drug reaction in association with the administration of rFVIIIFc, as defined by the Recommendations for Grading of Acute and Subacute Toxic Effects on the World Health Organization (WHO) scale [WHO Handbook 1979]:

    - Grade 2: bronchospasm; no parenteral therapy needed
    - Grade 3: bronchospasm; parenteral therapy required
    - Grade 4: anaphylaxis

5. The subject uses FVIII products other than rFVIIIFc (exception allowed for 1 emergency or accidental use).

6. The subject receives concomitant immunomodulation.

7. The subject develops any condition that precludes him from complying with the study procedures.

8. The subject experiences a medical emergency that necessitates discontinuation of treatment.

9. It is not in the subject's best interest to continue with the study treatment, in the judgment of the Investigator.

10. The parent/legal guardian decides to withdraw the subject from the study.

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

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

For any subject who is not responding to treatment with rFVIIIFc, as determined by the Investigator, a decision will be made with the Bioverativ Medical Monitor whether to continue the subject in the study. If the decision is made to withdraw the subject from the study, the ET/EOT Visit assessments will be performed as described in Section 4.2.2.1 and Section 10.6.

12. STUDY TREATMENT MANAGEMENT

Study site staff should follow the DHA, which contains specific instructions on the handling, preparation, administration, and disposal of rFVIIIFc. **The DHA supersedes all other references (e.g., Investigator's Brochure, Protocol).**

The study treatment, rFVIIIFc, 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 12.1.4.

Study treatment must be dispensed only by a pharmacist or medically qualified staff. Study treatment is to be dispensed only to parents/legal guardians of subjects enrolled in this study or Sponsor-approved designees. 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 after preparation of a dose should not be used for another subject.

12.1. rFVIIIFc (BIIB031)

rFVIIIFc is supplied in a kit that contains several components, including, but not limited to, lyophilized drug, a diluent, a vial adapter, and an infusion set (see DHA for further details). The lyophilized drug product is provided in 4 different strengths in a glass vial containing 250, 500, 1000, or 2000 IU of rFVIIIFc per vial. In addition to the rFVIIIFc, the formulation of the lyophilized drug product contains [redacted] L-histidine, [redacted] sodium chloride, [redacted] calcium chloride dihydrate, [redacted] sucrose, and [redacted] polysorbate 20 and is the same for all 4 strengths. The diluent is sterile water for injection for reconstitution of rFVIIIFc prior to administration to subjects.

The label will comply with local labeling requirements.

12.1.1. rFVIIIFc Preparation

At the first visit when study product is given, the individual preparing the study treatment should first carefully review the instructions provided in the DHA before preparing the dose assigned for the subject.

The pharmacist or medically qualified staff member will provide the Investigator or clinical staff with enough rFVIIIFc kits for treatment until the subject's next clinic visit. This will be documented according to Section 12.1.4.

If the packaging is damaged, or if there is anything unusual about the appearance or attributes of the vials of rFVIIIFc or syringes containing the diluent, it should not be used. The vial or syringe in question should be saved at the study site and the problem immediately reported to the Clinical Monitor.

12.1.2. rFVIIIFc Storage at Site

The study treatment, rFVIIIFc, must be stored in a secure location. The rFVIIIFc kit should be stored on site at 2°C to 8°C in a monitored and locked refrigerator with limited access. If the refrigerator does not have a lock, the refrigerator must be located in a locked room. For the most up-to-date storage requirements, follow the instructions provided in the DHA.

12.1.3. rFVIIIFc Handling and Disposal

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

If any Bioverativ supplies are to be destroyed at the study site, the institution or appropriate site personnel must obtain prior approval from Bioverativ, by providing, in writing, the destruction policy or details of the method of destruction. After such destruction, Bioverativ must be notified, 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.

12.1.4. rFVIIIFc Accountability

Accountability for study treatment is the responsibility of the Investigator. The study site must maintain accurate records demonstrating dates 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 should 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 Bioverativ. A written explanation must be provided to Bioverativ for any discrepancies.

13. EFFICACY AND PHARMACOKINETIC ASSESSMENTS

See Section 4.2 for the timing of assessments.

13.1. Clinical Efficacy Assessments

The following clinical tests/assessments will be performed to assess the efficacy of rFVIIIFc:

- Recording of bleeding episodes at Baseline IR Visit, other clinic visits, and during hospitalizations in the eCRF by the Investigator; recording of all other bleeding episodes in the EPD by the parent or caregiver.
- Assessment of response to bleeding episodes using the 4-point scale by the Investigator for individual bleeding episodes treated in the clinic; assessment of all other bleeding episodes in the EPD by the parent or caregiver. See Appendix B.
- Physician's global assessment of the subject's response to his treatment regimen using the 4-point scale. See Appendix D.

13.2. Laboratory Efficacy Assessments

Not applicable.

13.3. Pharmacokinetic Assessments

Samples are to be collected for PK assessments before and after the rFVIIIFc injection at the Baseline IR Visit, and at all Interim Visits during the prophylaxis regimen when rFVIIIFc is administered in the clinic. Samples collected will be analyzed for FVIII activity at a central laboratory. Procedures for collecting, processing, storing, and transporting to the central laboratory are fully described in the Study Laboratory Manual.

For subjects undergoing surgery, samples are to be collected according to the schedule in Section 4.2.2.6. While hospitalized, blood will be drawn daily to be tested at the local laboratory for FVIII activity so that monitoring of the subject can occur in real time.

For subjects undergoing ITI, FVIII activity for trough level assessments is to be taken at each visit. FVIII activity for IR assessments while the subject is inhibitor positive is at the discretion of the Investigator. After a confirmed negative inhibitor in subjects undergoing ITI, samples are to be collected for the calculation of IR and assessment of $t_{½}$ according to the schedule shown in Section 4.2.2.3. See Section 10.2.7 for details of assessments. Samples collected will be analyzed for FVIII activity at a central laboratory.

See Section 4.2 for the timing of assessments.

13.4. Additional Assessments

13.4.1. Factor VIII Genotyping (Optional)

There is 1 target gene for hemophilia A. The name of the target gene is F8. Genotyping may provide information regarding the predisposition of genotypic subpopulations to experience different bleeding frequencies. The development of an inhibitor to treatment with factor concentrates is the single most serious complication of factor replacement. One of the decisive risk factors for the development of inhibitors is the type of mutation (e.g., full or missense) that codes for a protein that may be absent, truncated, or present but not functional. There is a correlation between the resultant protein and the likelihood of developing inhibitors to factor replacement [Oldenburg and Pavlova 2006].

For subjects whose F8 genotype is not known, a sample will be drawn for analysis at the Baseline IR Visit (or at a subsequent visit if blood volume is limiting at the Baseline IR Visit [Section 4.2.1 and Section 4.2.2.1]). Genotyping requires separate consent from the subject's parents/legal guardians. This is not an inclusion or exclusion criterion; refusal of the subject's parents/legal guardians, or local laws precluding this test, would not exclude the subject from the study. The subject's parent/legal guardian may provide consent in order to receive this testing at any time during the Treatment Period.

The central laboratory will provide genotyping kits to the sites. The central laboratory will receive and forward the genotyping samples to Puget Sound Blood Center Hemostasis Reference Laboratory at periodic intervals for analysis. Analysis will take approximately 1 month, and the Investigator at the site will be informed of the result.

Additionally, residual blood cell pellets (buffy coat and erythrocytes) from plasma samples will be archived and may be used, if clinically or scientifically indicated, for [redacted] Genotyping samples will be retained indefinitely (unless prohibited by local law).

13.4.2. Whole Blood for Exploratory Assays for Inhibitor Positive Subjects

Whole blood samples will be collected to [redacted] in inhibitor positive subjects. Samples will be taken at the following time points: at the pre-ITI assessment visit; every other month during ITI; at the declaration of success, partial success or failure; and at the end of tapering (if applicable). A minimum of 3 mL and a maximum of 10 mL of whole blood should be collected at each time point, as allowable by patient weight and institutional practice regarding blood draw restrictions for pediatric patients. These samples will be stored indefinitely (unless prohibited by local law). [redacted]

13.4.3. Health Outcomes Related to Hemophilia

Assessments of health outcomes related to hemophilia may include:

- Number of hemophilia-related hospitalizations, excluding planned hospitalizations documented at screening
- Number of hemophilia-related hospitalization days
- Number of hemophilia-related emergency room visits
- Number of hemophilia-related physician visits excluding study visits
- Number of days off school or day care (kindergarten)
- Number of days off work for parent/legal guardian or caregiver (demographic data for caregivers may be collected at the Screening Visit)
- Primary method of administering rFVIIIFc

14. SAFETY ASSESSMENTS

See Section 4.2 for the timing of assessments.

14.1. Clinical Safety Assessments

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

- Physical examination
- Medical and surgical history
- Height
- Weight
- Vital sign measurements (blood pressure, pulse rate, respiratory rate, and temperature)
- Concomitant therapy and procedure recording, including concomitant medications taken by the mother of any subject who is receiving breast milk, unless the breast milk is derived from a source other than the mother or the mother has not consented.
- AE and SAE recording

See Section 4.2 for the timing of assessments.

14.2. Laboratory Safety Assessments

The following laboratory tests will be performed to evaluate the safety profile of rFVIIIFc. All samples will be analyzed at a central laboratory. Procedures for collection, processing, storing, and transporting the samples are fully described in the Study Laboratory Manual.

- Hematology: white blood cell count and differential, red blood cell, hemoglobin, hematocrit, and platelet count
- Blood chemistry: sodium, potassium, chloride, total protein, total bilirubin, gamma glutamyl transferase, aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, blood urea nitrogen, serum creatinine, and glucose

Subjects of low body weight may require screening blood draws over multiple days in order to comply with maximum allowable blood draw volumes [European Commission 2008]. 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.

14.3. rFVIIIFc-Specific Safety Assessments

The following assessments will be performed to determine the safety of rFVIIIFc:

- Neutralizing antibody development (inhibitor) measured by the Nijmegen-modified Bethesda assay

See Section 4.2 for the timing of assessments.

14.4. Archive Samples

14.4.1. Archive Plasma Samples

Primary and backup plasma samples from each subject obtained at each sampling time point for inhibitor and anti-rFVIIIFc testing will be will be aliquoted into 2 vials where possible. These 2 aliquots will be shipped to the central laboratory in separate shipments (the second aliquot being a back-up sample in case of damage or loss during shipping). Where the backup sample is not used, it will be stored (archived) and may be used, if clinically or scientifically indicated, for the following:

1. Testing for coagulation parameters
2. Lupus anticoagulant
3. Additional testing in the event that a subject develops an inhibitor, or is suspected of having developed an inhibitor, or has an anaphylactic reaction to the study treatment
    - In the event of a subject developing an inhibitor to rFVIIIFc (titer ≥0.60 BU/mL), additional testing will include FVIII-specific inhibitors
4. Testing for immunology or further coagulation assays or for clarification of any clinical or laboratory AE

In addition to this, a portion of the above samples will continue to be archived until after completion of review by competent authorities in accordance with EMA guidance [EMA (EMA/CHMP/BPWP/144533/2009) 2011] in the case of a positive inhibitor or clinical suspicion of inhibitor.

14.4.2. Archive Genotyping Samples (Optional)

Residual blood cell pellets (buffy coat and erythrocytes) from plasma samples for genotyping at baseline or the first interim visit (see Section 13.4.1) will be archived and may be used, if clinically or scientifically indicated, [redacted]

Genotyping samples will be retained indefinitely (unless prohibited by local law).

14.4.3. Sample Volumes

The volume of blood taken from the subjects should comply with European Commission guidance [European Commission 2008], namely the study-related blood loss should not exceed 3% of the total blood volume during a period of 4 weeks and should not exceed 1% at any single time. Examples of recommended blood draw volume limits per the European Commission guidance are provided in Table 2. Local and/or regional guidelines regarding blood draw volumes may also apply.

Subjects weighing <6 kg may require screening blood draws over multiple days in order to comply with maximum allowable blood draw volumes [European Commission 2008]. 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.

Table 2: Examples of Recommended Blood Draw Volume Limits

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

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

[b] Based on European Commission guidance [European Commission 2008] recommending that blood draw volumes not exceed 1% of total blood volume on a single occasion or 3% over a 4-week 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 informed consent form (ICF), each subject's 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.

15.1. Definitions

15.1.1. Adverse Event

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

Bleeding episodes in this patient population are not considered as AEs. Bleeding episodes that meet a serious criterion (see Section 15.1.2) should be reported as an SAE. All bleeding episodes after the Baseline IR Visit will be captured in the EPD that the subject's parents/caregivers will be maintaining throughout the study period.

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 inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity, or
- 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 one 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 an inpatient hospitalization.)

15.1.2.1. Serious Pretreatment Event

A serious pretreatment event is any event that meets the criteria for SAE reporting (as defined in Section 15.1.2) and occurs after the subject's parents/legal guardians sign the ICF, but before administration of study treatment. A serious pretreatment event is to be recorded on the SAE Form and faxed to Quintiles Pharmacovigilance within 24 hours of the study site staff becoming aware of the event (see Section 15.3.3).

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 for 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 Study Treatment	
Not related	An adverse event will be considered "not related" to the use of the investigational drug if there is not a reasonable 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 adverse event (e.g., the event occurred before administration of drug), or the presence of a more likely alternative explanation for the adverse event.
Related	An adverse event will be 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 rechallenge, 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 adverse event, or a lack of an alternative explanation for the 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; symptoms 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 according to the Investigator's Brochure for rFVIIIFc.

15.3. Monitoring and Recording Events

15.3.1. Adverse Events

Any AE experienced by the subject between the time of first dose of study treatment and the Safety Follow-up Visit/Telephone Call is to be recorded on the eCRF, regardless of the severity of the event or its relationship to study treatment. All AEs experienced by the subject should be followed up until they have resolved, stabilized, or returned to baseline in subsequent visits.

In addition, any known, untoward event that occurs subsequent to the AE reporting period that the Investigator assesses as possibly related to the investigational medication/product should also be reported as an AE.

15.3.2. Serious Adverse Events

Any SAE experienced by the subject between the time of signing 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 Quintiles Pharmacovigilance and the designated personnel within 24 hours as described in Section 15.3.3. Follow up information regarding an SAE must be reported within 24 hours.

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:

- A subject develops an inhibitor, as defined in Section 10.2.5.

- 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 WHO scale [WHO Handbook 1979]:
  - Grade 2: bronchospasm; no parenteral therapy needed
  - Grade 3: bronchospasm; parenteral therapy required
  - Grade 4: anaphylaxis
- A subject develops a vascular thrombotic event in association with the administration of rFVIIIFc, with the exception of IV injection site thrombophlebitis
- A subject undergoes major surgery

Allergic reactions, including anaphylaxis, have been reported with FVIII products. The subject's parents/caregivers (and the subject, if applicable) should be informed of early symptoms and signs of hypersensitivity reactions, including difficulty breathing, chest tightness, swelling of the face, rash, or hives. If such an event occurs while the subject is at home, the parents/caregivers should be instructed to seek immediate medical care for the subject.

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

15.3.3. Immediate Reporting of Serious Adverse Events

In order to adhere to all applicable laws and regulations for reporting an SAE, the study site must formally notify Quintiles 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 Serious Event that occurs between the time that the parents/legal guardians have signed the informed consent and 7 to 14 days after the last dose of rFVIIIFc (up to final safety follow-up visit/telephone call) must be reported to Quintiles 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 a Serious Event, fax a completed SAE form to Quintiles Pharmacovigilance at the country-specific fax numbers provided in the Study Reference Manual.

Any SAE must also be entered in the eCRF in the same timeframe.

15.3.3.1. Deaths

Death is an outcome of an event. The event that resulted in death should be recorded and reported 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 Quintiles Pharmacovigilance. The term death should 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 Bioverativ to be related to the study treatment administered.

Bioverativ (or designee) will report SUSARs to the appropriate regulatory authorities and Investigators, according to local law.

15.4. Procedures for Handling Special Situations

15.4.1. Overdose

For the purposes of this study, any prophylactic dose greater than 150 IU/kg will be considered an overdose. Doses greater than 150 IU/kg will not be considered overdoses if they are given as part of episodic treatment, treatment of a bleeding episode, surgical management, or during the ITI regimen.

Overdoses are not considered AEs; however, all overdoses should be recorded on an Overdose Form and faxed to Quintiles Pharmacovigilance within 24 hours. An overdose should be reported even if it does not result in an AE. Overdoses do not need to be recorded in the eCRF; dosing information is recorded in the eCRF.

15.4.2. 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) should contact the Study's Medical Director. Refer to the Study Reference Guide's Official Study Contact List for complete contact information.

15.4.3. Unblinding for Medical Emergencies

Not applicable.

15.5. Safety Responsibilities

15.5.1. Investigator Responsibilities

The Investigator's responsibilities include the following:

- 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.
- Complete an SAE form for each serious event and fax it to Quintiles Pharmacovigilance within 24 hours of the study site staff becoming aware of the event.
- Pursue SAE follow-up information actively and persistently. Follow-up information must be reported to Quintiles Pharmacovigilance within 24 hours of the study site staff becoming aware of new information.
- Ensure all AE and SAE reports are supported by documentation in the subjects' medical records.
- Pursue AE and SAE follow-up information until the event has resolved or become stable.
- Report SAEs to local ethics committees, as required by local law.

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 should maintain a list of the appropriately qualified persons to whom significant study-related duties have been delegated.

15.5.2. Bioverativ Responsibilities

Bioverativ'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 AEs and SAEs.

- Bioverativ 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

In general, all statistical analyses will be descriptive in nature. No formal comparison is planned and no hypothesis will be formally tested. Continuous variables will be summarized and presented by the number of observations, mean, median, standard deviation, minimum, and maximum. Categorical variables will be summarized by the number and percentage in each category.

The objectives and endpoints are as described in Section 6.

16.1. Demography and Baseline Disease Characteristics

The analysis of demography and baseline disease characteristics will be based on the Safety Analysis Set. A description of the Safety Analysis Set is provided in Section 16.5.1. Demographics and baseline disease characteristics will be summarized categorically and/or with descriptive statistics, as appropriate.

Demographic data to be tabulated will include, but not be limited to, age, race, weight, and geographic location.

Baseline disease characteristics, based on general medical and surgical, hemophilia, and bleeding histories, will be summarized as follows. General medical and surgical history will be summarized by the number and percentage of subjects with a medical history in each of the major body system classifications. Hemophilia history data to be tabulated will include but not be limited to genotype, types of blood products previously used, and other disease- and treatment-specific measures. Bleeding history will include a summary of the number and types of bleeding episodes subjects experienced during the 3 months prior to this study.

16.2. Efficacy

16.2.1. Analysis Population

Subjects who receive at least 1 dose of rFVIIIFc will be included in the Full Analysis Set (FAS). Efficacy analyses will be based on the FAS, including the data collected on or after the time of the first injection of rFVIIIFc study drug.

Subjects developing a confirmed positive inhibitor test after exposure to rFVIIIFc (the Inhibitor Subgroup) will have their efficacy data included up to the time of the last negative inhibitor test; efficacy data collected after the time of the last negative inhibitor test will be summarized separately.

16.2.2. General Methods of Analysis

All efficacy endpoints are secondary. No imputation will be applied to any missing efficacy data.

The efficacy and surgical/rehabilitation periods will be defined in the statistical analysis plan (SAP) for the purpose of determining the study periods during which data will be used for select efficacy analyses. Data on bleeding and rFVIIIFc consumption will be based on the efficacy period; surgical evaluations will be based on the surgical/rehabilitation period.

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

16.2.3. Analysis of Efficacy Endpoints

Annualized Bleeding Episodes and Annualized rFVIIIFc Consumption

Bleeding episodes during the efficacy period will be annualized on a per-subject basis and summarized by treatment regimen (episodic or prophylaxis regimen) and overall. This annualized bleeding rate (ABR) will be calculated as the total number of bleeding episodes experienced by a subject divided by the total number of days in their efficacy period for each treatment regimen or overall as appropriate, multiplied by 365.25. The per-subject ABR will also be summarized for type of bleed (spontaneous or traumatic), location of the bleed, and spontaneous joint bleeding episodes, and for other subgroups of interest. The consumption of rFVIIIFc will be annualized in a similar fashion and summarized overall as well as for subgroups of interest.

Other Efficacy Endpoints

The number of injections and dose per injection required to resolve bleeding will be summarized on both a per-bleeding-episode and a per-subject basis, where the per-subject basis will be determined as the average over all bleeding episodes for a given subject.

The response to treatment for bleeding will be summarized by the number and percentage of bleeding episodes with each response (excellent, good, moderate, or none).

These data will be summarized overall and for subgroups of interest.

Other Efficacy Assessments

The total dose administered to resolve a bleeding episode will be calculated and summarized in addition to, and in the same manner as, the specified endpoints of number of injections and dose per injection for resolution of bleeding.

The Investigator's assessment of the subject's overall response to his rFVIIIFc regimen will be summarized for each study visit and across all visits for the number and percentage of outcomes classified as excellent, effective, partially effective, and ineffective. Summaries will be provided overall.

Treatment with rFVIIIFc, bleeding episodes, blood loss, and transfusions administered for major and minor surgeries will be provided in data listings. These assessments will be made during the

various components of the surgical/rehabilitation period as appropriate (surgery, postoperative care, and rehabilitation).

16.2.4. Additional/Exploratory Analysis of Efficacy Endpoints

Other efficacy analyses may be conducted for exploratory purposes, including summary of exploratory endpoints (health outcomes, Investigator/Surgeon's Assessment of Response).

16.3. Pharmacokinetics

IR data will be listed and summarized by visit. For each subject, the observed IR estimated at each applicable visit will be averaged and summarized.

PK parameters, such as IR and $t_{½}$, derived from assessments during ITI will be listed for each applicable subject. PK parameters (IR and $t_{½}$) for subjects undergoing ITI will be determined by real-time analyses of the FVIII activity data measured by the one-stage clotting assay to facilitate assessment of ITI outcome.

16.4. Pharmacodynamics

Not applicable.

16.5. Safety

Unless specified otherwise in the SAP, safety data will be summarized overall. Subjects developing a confirmed positive inhibitor test after exposure to rFVIIIFc study drug (the Inhibitor Subgroup) will have their safety data included up to the time of the last negative inhibitor test; safety data collected after the time of the last negative inhibitor test will be summarized separately.

16.5.1. Analysis Population

The Safety Analysis Set is defined as all subjects who receive at least 1 dose of rFVIIIFc study drug. Safety analyses will be based on the Safety Analysis Set, including the data collected on or after the time of the first injection of rFVIIIFc.

16.5.2. Methods of Analysis

16.5.2.1. Occurrence of Inhibitor Development

The proportion of subjects who develop an inhibitor during the study will be determined along with the exact (Clopper-Pearson) 2-sided, 95% confidence interval. Any subject who develops an inhibitor following the initial rFVIIIFc administration will be included in the numerator; however, only subjects with a valid inhibitor test following at least 10 EDs of rFVIIIFc study drug will be included in the denominator. One ED is defined as a 24-hour period in which a subject receives 1 or more doses of rFVIIIFc, with the time of the first injection of rFVIIIFc defined as the start of the ED.

16.5.2.2. Adverse Events

AEs will be coded using the Medical Dictionary for Regulatory Activities. The incidence of AEs will be summarized by system organ class and preferred term. Summaries will be for all AEs as well as by severity and relationship to treatment. Subject listings will be provided for all AEs, SAEs, AEs resulting in discontinuation of study treatment and/or from the study, and deaths. Unless otherwise specified in the study SAP, AEs and SAEs occurring during treatment with the ITI regimen will be summarized and listed separately.

16.5.2.3. Other Safety Parameters

Clinical laboratory values will be summarized for change from baseline, shifts, and potentially clinically significant abnormalities. Threshold levels for potentially clinically significant laboratory abnormalities will be provided in the SAP. Listings of abnormal laboratory test results will be provided.

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

Duration of exposure and the total number of EDs to rFVIIIFc per subject will be summarized overall based on the Safety Analysis Set.

16.6. Immune Tolerance Induction

For each subject undergoing ITI, the outcome (complete success, partial success, failure, and early withdrawal during the monitoring period will be listed and summarized. Additional summaries, including the percentage of subjects with relapse (as defined in Section 10.2.7.6), will be documented in the study SAP.

16.7. Interim Analyses

An interim analysis of safety and efficacy data will be conducted when at least 50 subjects have completed at least 50 EDs and undergone inhibitor testing. Additional interim analyses may be conducted during the study, as needed. Analyses will be descriptive in nature. No formal comparisons are planned, and no hypotheses will be formally tested.

16.8. Sample Size Considerations

Because the size of the hemophilia population is limited, the sample size is based on clinical rather than statistical considerations. Taking into account the CHMP Guideline [EMA (EMA/CHMP/BPWP/144533/2009) 2011] and in an effort to enroll a sufficient number of subjects to assess the efficacy and safety of rFVIIIFc in this population of primarily very young children, approximately 105 subjects will be dosed with rFVIIIFc to achieve at least 90 subjects with no less than 50 EDs by the completion of the study.

17. ETHICAL REQUIREMENTS

Bioverativ and the Investigator must comply with all instructions, regulations, and agreements in this protocol and applicable ICH and 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 and GCP guidelines. The Investigator should 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, informed consent form (ICF), and other required study documents prior to starting the study. Bioverativ will submit documents on behalf of the investigational sites in countries other than the United States.

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

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

Bioverativ must receive a letter documenting ethics committee approval, which specifically identifies the protocol, protocol number, and ICF, 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.

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

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's legally authorized representative, as applicable, in accordance with local practice and regulations. Consent must also be obtained from breastfeeding mothers of subjects.

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's parents/legal guardians. The subject's parents/legal guardians must be given sufficient time to consider whether to participate in the study.

Subjects' parents/legal guardians will be informed that the subject's race and ethnicity will be collected and will be used during analysis of study results. (See Section 17.4.)

A copy of the ICF, signed and dated by the subject's parents/legal guardians, must be given to them. Confirmation of a subject's legally authorized representative'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.

Each consent form should contain an authorization allowing the Principal Investigator(s) and Bioverativ to use and disclose PHI (that is, subject-identifiable health information) in compliance with local law.

The signed consent form 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 (including study subjects and their breastfeeding mothers, if applicable) must also provide all authorizations required by local law (e.g., PHI authorization in North America).

During the study, subjects' race and ethnicity will be collected. These data may be used in the analysis of the safety and/or pharmacokinetic profile of the study treatment. In cross sectional analyses of different ethnic groups, differences in the occurrence of inhibitors have been observed [Astermark 2005; Carpenter 2012]. Differential responses to Factor VIII products may occur in different haplotypes of FVIII that also differ across racial and ethnic groups [Viel 2009].

The subject will not be identified by name in the eCRF or in any study reports, and these reports will be used for research purposes only. Bioverativ, its partner(s) and designee(s), 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

Bioverativ maintains appropriate insurance coverage for clinical trials and will follow applicable local compensation laws.

17.6. Conflict of Interest

The Investigators should address any potential conflicts of interest (e.g., financial interest in Bioverativ) with the subject before the subject makes a decision to participate in the study.

17.7. Registration of Study and Disclosure of Study Results

Bioverativ will register the study and poststudy results regardless of outcome on a publicly accessible website in accordance with the 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 Bioverativ or designee. This 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 Bioverativ 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

The Investigator must permit study-related monitoring by providing direct access to source data and to the subjects' medical histories.

The Clinical Monitor(s) will visit the Investigator(s) at regular intervals during the study and after the study has completed, as appropriate.

During these visits, eCRFs and supporting documentation related to the study will be reviewed and any discrepancies or omissions will be resolved.

Monitoring visits must be conducted according to the applicable ICH and GCP guidelines to ensure protocol adherence, quality of data, study treatment accountability, compliance with regulatory requirements, and continued adequacy of the investigational site and its facilities.

18.4. Study Funding

Bioverativ is the Sponsor of the study and is funding the study. All financial details are provided in the separate contract(s) between the institution, Investigator, and Bioverativ

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 contract research organization (CRO) will be responsible for administrative aspects of the study including, but not limited to, study initiation, monitoring, management of SAE reports, data management, and the coordination of an independent external DSMC. 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 Voice and Web Response System

An IXRS will be used in this study. Before subjects are screened or enrolled, the appropriate training will be provided to the study staff by Bioverativ and the IXRS vendor. A user manual will also be provided. Specific details regarding IXRS are provided in the Study Reference Manual.

19.1.3. Electronic Data Capture

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

Subjects' 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 no more than 7 days (Section 10.2.4.1.4).

19.1.4. Central Laboratories for Laboratory Assessments

Central laboratories have been selected by Bioverativ to analyze all the laboratory samples being collected in the study. Specifics regarding the requirements for laboratory specimen collection, handling, and analysis are provided in the Laboratory Manuals.

19.2. Study Committees

19.2.1. Independent Data Safety Monitoring Committee

An independent, external DSMC is responsible for evaluating and monitoring the safety and tolerability of the study drug on an ongoing basis during the study. The specifics regarding the DSMC organization and procedures will be outlined in the DSMC Charter.

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, Bioverativ 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 subsequent to the modification.

In the event of a protocol modification, the ICF may require similar modifications (see Sections 17.2 and 17.3).

19.4. Ethics Committee Notification of Study Completion or Termination

Where required, the regulatory 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 Bioverativ in writing and receive written authorization from Bioverativ to destroy study records. In addition, the Investigator must notify Bioverativ of any changes in the archival arrangements including, but not limited to, archival at an offsite facility or transfer of ownership if the Investigator leaves the site.

19.6. Study Report Signatory

Bioverativ 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 Bioverativ.

Bioverativ will follow all applicable local regulations pertaining to study report signatories.

20. REFERENCES

Astermark J, Oldenburg J, Escobar M, et al. The Malmö International Brother Study (MIBS). Genetic defects and inhibitor development in siblings with severe hemophilia A. Haematologica. 2005;90(7):924-31.

Aznar JA, Magallón M, Querol F, et al. The orthopaedic status of severe haemophiliacs in Spain. Haemophilia. 2000;6(3):170-6.

Berntorp E, Boulyjenkov V, Brettler D, et al. Modern treatment of haemophilia. Bull World Health Organ. 1995;73(5):691-701.

Bolton-Maggs PH, Pasi KJ. Haemophilias A and B. Lancet. 2003;361(9371):1801-9.

Carpenter SL, Michael Soucie J, Sterner S, et al. Increased prevalence of inhibitors in Hispanic patients with severe haemophilia A enrolled in the Universal Data Collection database. Haemophilia. 2012;18(3):e260-5.

Colvin BT, Astermark J, Fischer K, et al. European principles of haemophilia care. Haemophilia. 2008;14(2):361-74.

Dumont JA, Low SC, Peters RT, et al. Monomeric Fc fusions: impact on pharmacokinetic and biological activity of protein therapeutics. BioDrugs. 2006;20(3):151-60.

European Medicines Agency. Guideline on the clinical investigation of recombinant and human plasma-derived factor VIII products. EMA/CHMP/BPWP/144533/2009. July 21, 2011. http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2011/08/WC500109692.pdf.

European Commission. Ethical considerations for clinical trials on medicinal products conducted with the paediatric population. 2008. p. 34.

Ghetie V, Ward ES. Multiple roles for the major histocompatibility complex class I- related receptor FcRn. Annu Rev Immunol. 2000;18:739-66. Epub 2000/06/03.

Hay CRM, DiMichele DM. The principal results of the International Immune Tolerance Study: a randomized dose comparison. Blood. 2012;119(6):1335-1344.

Junghans RP, Anderson CL. The protection receptor for IgG catabolism is the beta2-microglobulin-containing neonatal intestinal transport receptor. Proc Natl Acad Sci U S A. 1996;93(11):5512-6.

Manco-Johnson MJ, Abshire TC, Shapiro AD, et al. Prophylaxis versus episodic treatment to prevent joint disease in boys with severe hemophilia. N Engl J Med. 2007;357(6):535-44.

Mannucci PM, Tuddenham EG. The hemophilias--from royal genes to gene therapy. N Engl J Med. 2001;344(23):1773-9.

MASAC Recommendation #179 Concerning Prophylaxis (Regular Administration of Clotting Factor Concentrate to Prevent Bleeding). November 2007 (Replaces #170). New York, NY: National Hemophilia Foundation. http://www.hemophilia.org/NHFWeb/Resource/StaticPages/menu0/menu5/menu57/masac179.pdf. Accessed December 03, 2012.

MASAC Recommendation #190 Concerning Products Licensed for the Treatment of Hemophilia and Other Bleeding Disorders. March 2009 (Replaced by Recommendation #215, November 2012). New York, NY: National Hemophilia Foundation. http://www.hemophilia.org/NHFWeb/Resource/StaticPages/menu0/menu5/menu57/masac190.pdf.

Molho P, Rolland N, Lebrun T, et al. Epidemiological survey of the orthopaedic status of severe haemophilia A and B patients in France. The French Study Group. secretariat.haemophiles@cch.ap-hop-paris.fr. Haemophilia. 2000;6(1):23-32.

Oldenburg J, Pavlova A. Genetic risk factors for inhibitors to factors VIII and IX. Haemophilia. 2006;12(Suppl 6):15-22.

Rodriguez-Merchan EC. Management of musculoskeletal complications of hemophilia. Semin Thromb Hemost. 2003;29(1):87-96.

Roopenian DC, Akilesh S. FcRn: the neonatal Fc receptor comes of age. Nat Rev Immunol. 2007;7(9):715-25. Epub 2007/08/19.

Valentino LA, Kempton CL, Kruse-Jarres R, et al. US Guidelines for immune tolerance induction in patients with haemophilia a and inhibitors. Haemophilia. 2015;21(5):559-67.

Viel KR, Ameri A, Abshire TC, et al. Inhibitors of factor VIII in black patients with hemophilia. N Engl J Med. 2009;360(16):1618-27.

Guidelines for the management of hemophilia. Montréal, Québec: World Federation of Hemophilia.

WHO. Handbook for reporting results of cancer treatment. Geneva, Switzerland: World Health Organization Offset Publication No. 48; 1979. http://whqlibdoc.who.int/offset/WHO_OFFSET_48.pdf. Accessed November 30, 2012.

21. SIGNED AGREEMENT OF THE STUDY PROTOCOL

I have read the foregoing protocol, "An Open-Label, Multicenter Evaluation of the Safety and Efficacy of Recombinant Coagulation Factor VIII Fc Fusion Protein (rFVIIIFc; BIIB031) in the Prevention and Treatment of Bleeding in Previously Untreated Patients With Severe Hemophilia A," and agree to conduct the study according to the protocol and the applicable ICH guidelines and GCP 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. rFVIIIFc DOSING GUIDELINES FOR BLEEDING EPISODES

The following table describes the recommended target activities of rFVIIIFc for bleeding episodes.

DOSING GUIDELINES FOR rFVIIIFc THERAPY IN HEMOPHILIA A

Type of Hemorrhage	Factor VIII Level Required (%)
Minor	
Epistaxis	20-40
Hemarthroses, uncomplicated	20-40
Superficial muscular	20-40
Superficial soft tissue	20-40
Moderate	
Epistaxis	30-60
Intramuscular with dissection	30-60
Soft tissue with dissection	30-60
Mucous membranes	30-60
Dental extractions	30-60
Hematuria	30-60
Hemarthroses, with limited motion	40-80
Major	
Epistaxis	80-100
Pharynx	80-100
Retropharynx	80-100
Retroperitoneum	80-100
Surgery	80-100
Central Nervous System	80-100

[redacted]

[redacted]

APPENDIX E. OBJECTIVES AND THEIR ASSOCIATED ENDPOINTS AND ASSESSMENTS

Figure 3: Primary Objective, Endpoints and Assessments

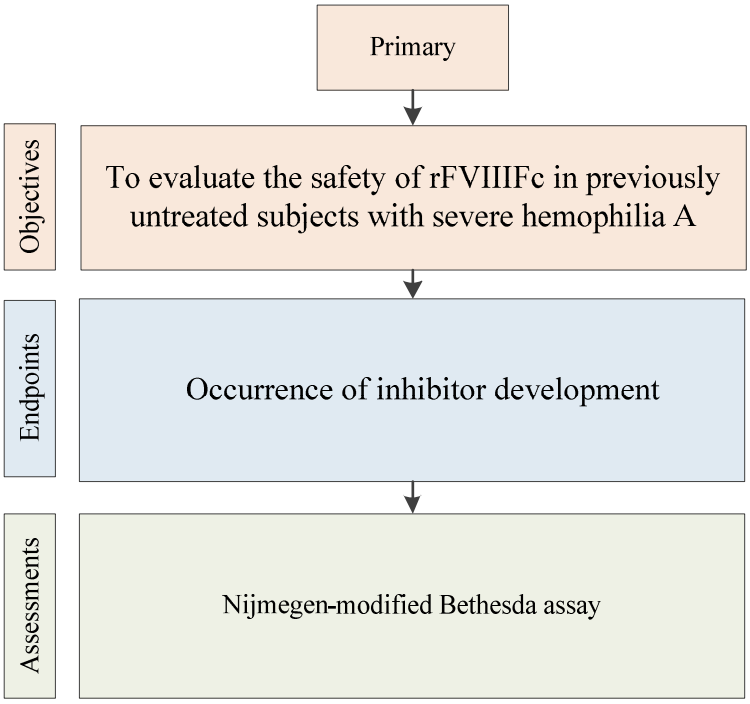


Figure 4: Secondary Objectives, Endpoints, and Assessments

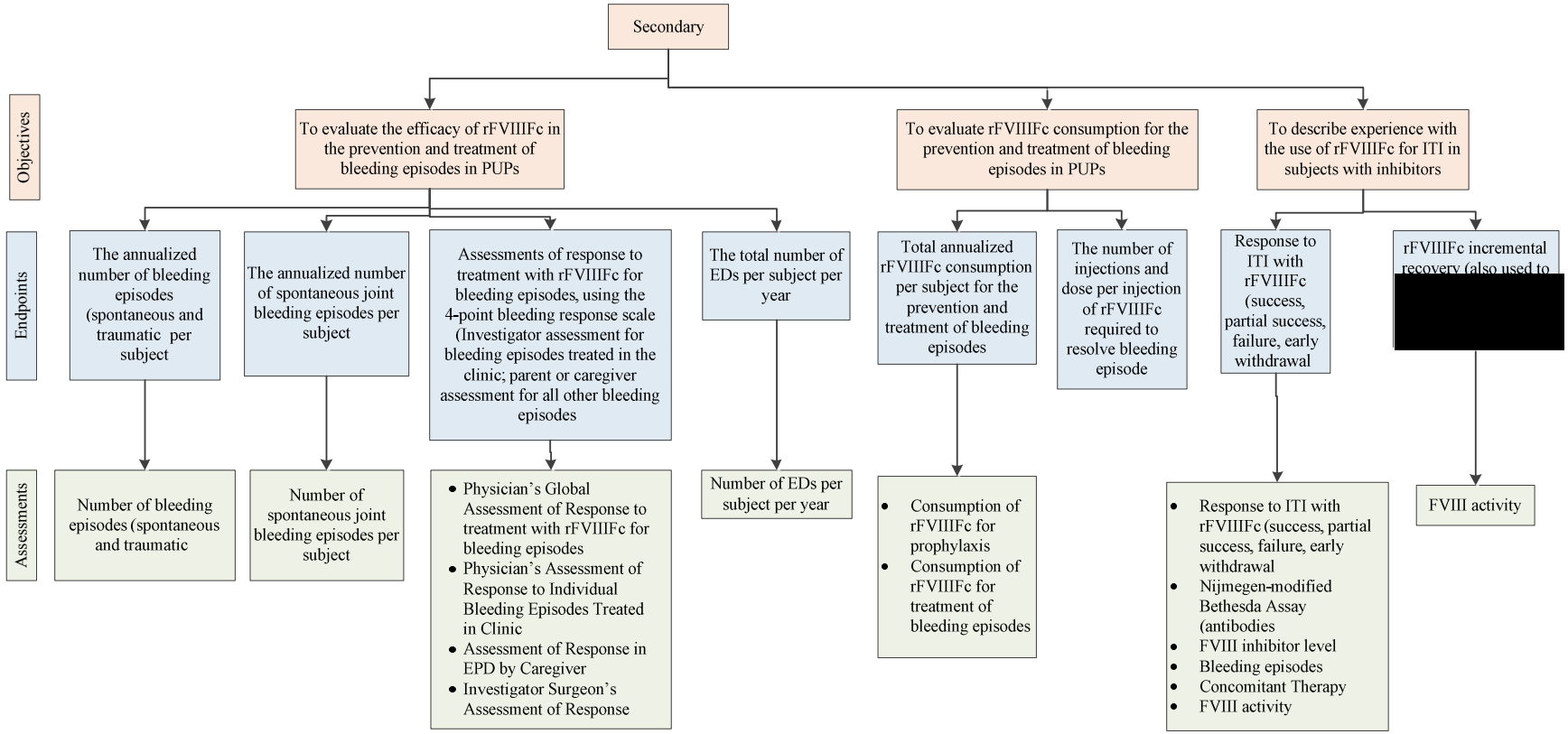


Figure 5: Exploratory Objectives, Endpoints, and Assessments