Bioverativ Therapeutics Inc.
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United States

PROTOCOL NUMBER: 998HB303

PHASE OF DEVELOPMENT: 3

PROTOCOL TITLE: An Open-Label, Multicenter Evaluation of the Safety and Efficacy of Recombinant Coagulation Factor IX Fc Fusion Protein (rFIXFc; BIIB029) in the Prevention and Treatment of Bleeding in Previously Untreated Patients With Severe Hemophilia B

EUDRA CT NO: 2013-003629-27

DATE: 06 August 2018
Version 3
FINAL

Supersedes previous Version 2 dated 28 February 2017.

SPONSOR SIGNATURE PAGE

Protocol 998HB303 was approved by:

[redacted]

06 Aug 18
Date

[redacted]
Bioverativ Therapeutics Inc.

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1. SPONSOR INFORMATION

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

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[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 AND DEFINITIONS

ABR	annualized bleeding rate
ADR	adverse drug reaction
AE	adverse event
BU	Bethesda unit
CHMP	Committee for Medicinal Products for Human Use
CI	confidence interval
CRO	contract research organization
DHA	Directions for Handling and Administration
DLT	dose-limiting toxicity
DSMC	Data Safety Monitoring Committee
eCRF	electronic case report form
ED	exposure day
EMA	European Medicines Agency
EOS	end of study
EPD	electronic patient diary
ET	early termination
FAS	Full Analysis Set
FcRn	neonatal Fc receptor
FIX	coagulation factor IX
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
IU	international units
IV	intravenous
IXRS	Interactive Voice/Web Response System
pdFIX	plasma-derived factor IX
PHI	protected health information
PK	pharmacokinetic, pharmacokinetics
PTP	previously treated patient
PUP	previously untreated patient
rFIX	recombinant coagulation factor IX
rFIXFc	recombinant coagulation factor IX Fc fusion protein
SAE	serious adverse event
SAP	statistical analysis plan
SUSAR	suspected unexpected serious adverse reaction
$t_{½}$	half-life
WHO	World Health Organization

3. SYNOPSIS

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

Protocol Number:	998HB303
Protocol Title:	An Open-Label, Multicenter Evaluation of the Safety and Efficacy of Recombinant Coagulation Factor IX Fc Fusion Protein (rFIXFc; BIIB029) in the Prevention and Treatment of Bleeding in Previously Untreated Patients With Severe Hemophilia B
Version Number:	3
Name of Study Treatment:	Recombinant coagulation factor IX Fc fusion protein (rFIXFc; BIIB029)
Study Indication:	Hemophilia B
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 IX (FIX) replacement therapies are limited by short elimination half-life requiring intravenous (IV) administration up to 3 times per week. The purpose of this study is to investigate the safety and efficacy of rFIXFc in previously untreated patients (PUPs) in accordance with the European Medicines Agency (EMA) Committee for Medicinal Products for Human Use (CHMP) guideline on clinical investigation of recombinant and human plasma-derived factor IX products [EMA (EMA/CHMP/BPWP/144552/2009) 2011].
Study Objectives and Endpoints:	**Objectives** The primary objective of the study is to evaluate the safety of rFIXFc in previously untreated subjects with severe hemophilia B.

The secondary objectives of the study are as follows:

- To evaluate the efficacy of rFIXFc in the prevention and treatment of bleeding episodes in PUPs.
- To evaluate rFIXFc consumption for prevention and treatment of bleeding episodes in PUPs.

The exploratory objective of the study is to evaluate the effect of rFIXFc based on patient-reported outcomes and health resource utilization.

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 (spontaneous and traumatic) per subject.
- the annualized number of spontaneous joint bleeding episodes per subject.
- assessments of response to treatment with rFIXFc for bleeding episodes, using the 4-point bleeding response scale (Investigator assessment for bleeding episodes treated in the clinic; parent or caregiver assessment for all other bleeding episodes).
- the total number of exposure days (EDs) per subject per year.
- total annualized rFIXFc consumption per subject for the prevention and treatment of bleeding episodes.
- the number of injections and dose per injection of rFIXFc required to resolve a bleeding episode.
- rFIXFc incremental recovery.

	The exploratory endpoints include, but are not limited to: • health outcomes
Study Design:	An open-label, single-arm, multicenter study evaluating the safety and efficacy of rFIXFc in previously untreated subjects with severe hemophilia B when used according to local standard of care for implementation of a prophylaxis regimen, including an optional preceding episodic (on-demand) treatment regimen. Following confirmation of eligibility, the Investigator has the option to treat the subject episodically before initiating a prophylaxis regimen. The duration of episodic treatment is at the Investigator's discretion, in accordance with local standard of care. The study will end when at least 20 subjects have reached at least 50 EDs with rFIXFc. Surgery is allowed during the study. Immune tolerance induction with rFIXFc is allowed during the study for those subjects developing a positive inhibitor after exposure to rFIXFc study drug if they have a positive low titer inhibitor that is not reliably controlled with rFIXFc or a positive high titer inhibitor. Adjustments to the dose and interval of rFIXFc can be made in this study based on available pharmacokinetic (PK) data, subsequent FIX activity levels, level of physical activity, and bleeding pattern, in accordance with local standards of care for a prophylactic regimen. Subjects may be enrolled and receive study drug after samples have been drawn for factor IX activity and inhibitor testing at the central laboratory, and diagnosis of severe hemophilia B with ≤2% factor IX activity has been established based on local laboratory values or in the documented medical record. However, any such subject must be withdrawn if the central laboratory screening results indicate factor IX activity >2%, or a positive inhibitor.
Rationale for Dose and Schedule Selection:	Results of the Phase 1/2a study (Study SYN-FIXFc-07-001) evaluating the safety and PK of a single dose of rFIXFc suggested that rFIXFc is well tolerated when given as a single dose at doses ranging from 1 to 100 international units (IU)/kg. In the completed Phase 3 study (Study 998HB102), multiple doses between 20 and

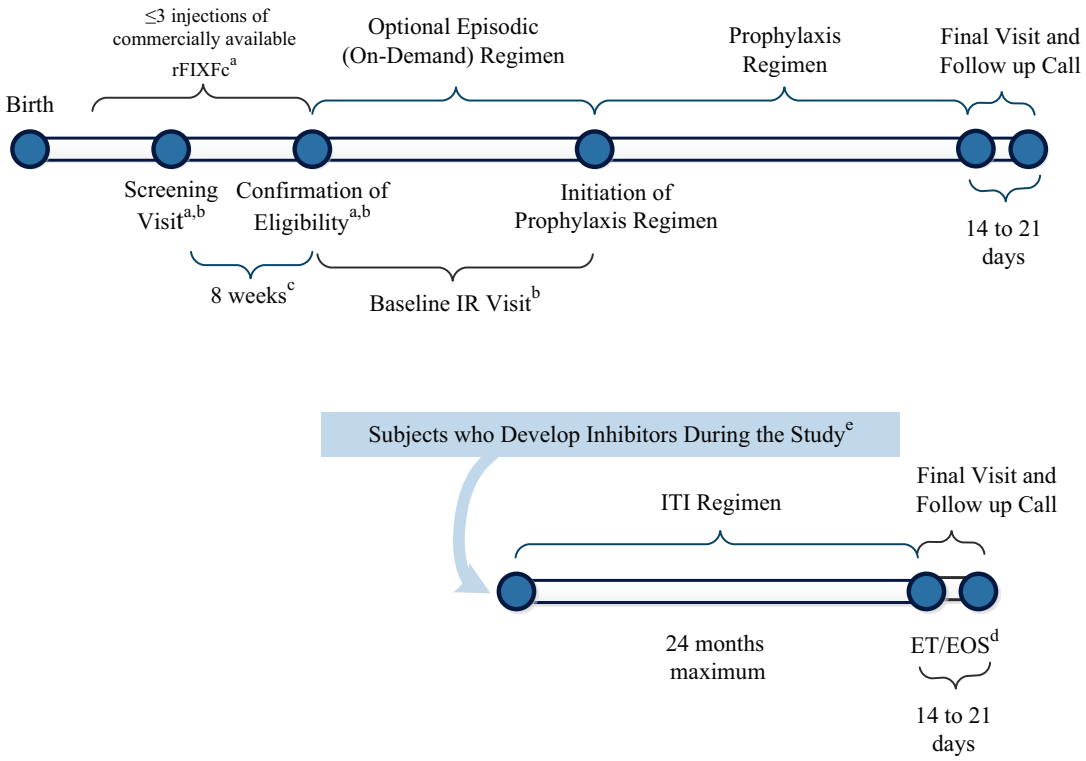
	100 IU/kg were generally well tolerated, with an adverse event profile generally consistent with that expected in patients with hemophilia B. The recommended starting prophylactic dose of rFIXFc in this study, approximately 50 IU/kg weekly, is based on the data from the Phase 1/2a and Phase 3 studies (including pediatric PK data from subjects <12 years of age) and knowledge of increased clearance and decreased recovery of factor concentrates in children. This dose is predicted to maintain trough levels >1% in 99% of pediatric subjects. The dose for treatment of bleeding episodes will target peak plasma FIX activity of approximately 30% to 100%, in accordance with local standards.
Study Location:	Multinational
Number of Planned Subjects:	At least 20 PUPs are expected to reach at least 50 EDs with rFIXFc at the end of the study.
Study Population:	This study will be conducted in male, previously untreated subjects <18 years of age with severe hemophilia B. Detailed entry criteria are described in the protocol.
Treatment Groups:	This is a single-arm study. Subjects developing inhibitors after exposure to rFIXFc study drug will enter the Inhibitor Subgroup.
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 withdrawal from the study occurs, or the end of study 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 rFIXFc (study drug and/or commercially available rFIXFc) will be included in the Safety Analysis Set. Subjects with at least 1 dose of rFIXFc

	study drug will be included in the Full Analysis Set (FAS). Subjects with at least 1 dose of rFIXFc study drug and who meet the eligibility criteria (with screening FIX activity and inhibitor test results confirmed by the central laboratory) will be included in the Supporting Analysis Set. Efficacy analyses will be based on the FAS. Safety analyses will be based on the Safety Analysis Set, with some analyses based on the Supporting Analysis Set, as appropriate. Subjects developing a confirmed positive inhibitor test after exposure to rFIXFc 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 bleeding episodes per person-year and 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:	No interim analyses are planned for this study.
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/144552/2009) 2011] and in an effort to enroll a sufficient number of subjects to assess the efficacy and safety of rFIXFc in this population of primarily very young children, approximately 30 subjects will be enrolled to achieve at least 20 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 determined by the Data Safety Monitoring Committee • detection of an unexpected, serious, or unacceptable risk to the study subjects

4. STUDY SCHEMATIC AND SCHEDULE OF EVENTS FOR STUDY 998HB303

4.1. Study Schematic

Figure 1: Study Design



EOS = end of study; ET = Early Termination; IR = incremental recovery; ITI = immune tolerance induction
[a] Subjects may not enter the study if they have received >3 injections of commercially available rFIXFc prior to confirmation of eligibility, or commercially available rFIXFc more than 28 days prior to the first Screening Visit.
[b] Screening Visit and Baseline IR Visit may be performed as 2 separate visits OR all activities necessary for screening, confirmation of eligibility, and the Baseline IR 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 scenario for the end of treatment is shown; however, the end of treatment may occur under other circumstances as defined by the protocol, for example, when the end of the study is declared or upon early withdrawal of a subject who does not meet the criteria for successful ITI (Section 10.2.6.4).
[e] See Section 10.2.6 for criteria of eligibility to receive the ITI regimen.

4.2. Schedule of Events

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

Tests and Assessments	Screening[a]	Baseline Incremental Recovery Visit[b]	
		Predose	Postdose
Informed Consent	X		
Demographics[c]	X		
Medical and Surgical History[d]	X		
Physical Examination[e]	X		
Height	X		
Weight	X	X	
Vital Signs[f]	X	X	X
Health Outcome		X	
Hematology[g]	X		
Blood Chemistry[h]	X		
Viral Analysis[i]	X		
Nijmegen-Modified Bethesda Assay (Inhibitor Assay)[j]	X[k]	X[l]	
FIX Activity	X[k]		
FIX Activity for Incremental Recovery[m]		X[l]	X
Anti-rFIXFc Antibody[j]	X	X[l]	
F9 Genotyping[n]		X	
Injection Site Inspection[o]			X
EPD Review, including rFIXFc Dosing Accountability[p]		Monitor and record at all visits	
rFIXFc Clinic Dosing		X	
Assessment of Response to Individual Bleeding Episodes in EPD by Subject/Parent/Caregiver[q]		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[r]	X	<<<<ONGOING: Monitor and record at all visits>>>>	
Serious Adverse Events[r]	X	<<<<ONGOING: Monitor and record at all visits>>>>	
Concomitant Therapy/Procedures Recording[s]	X	<<<<ONGOING: 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; F9 = target gene for hemophilia B; FIX = coagulation factor IX; HIV =

human immunodeficiency virus; ICF = informed consent form; IR = incremental recovery; rFIXFc = recombinant coagulation factor IX Fc fusion protein; SAE = serious adverse event

[a] If screening assessments cannot be completed within 8 weeks, some assessments may need to be repeated as described in Section 7.3.1.

[b] The Baseline IR Visit activities may be completed on the same day as Screening, or they may be completed as part of a separate visit (as shown) or at an unscheduled visit. Baseline IR requires a washout from rFIXFc of at least 72 hours prior to the predose sample collection.

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

[d] 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 dosing with commercially available rFIXFc for bleeding episodes between 28 days prior to Screening and meeting all eligibility criteria.

[e] After screening, physical examination should be performed at least annually; more frequent physical examinations may be performed at the Investigator's discretion, according to their standard of care.

[f] Vital signs include blood pressure, pulse rate, respiratory rate, and temperature (°C). Postdose assessments following in-clinic injections should be taken approximately 10 minutes after the end of the rFIXFc injection.

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

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

[j] Washout prior to sample collection for inhibitor and anti-rFIXFc antibody tests should be at least 72 hours (including prior to collection of the Screening sample, if there was prior dosing with FIX). Samples for anti-rFIXFc antibody testing will be collected at the same timepoint when any samples are collected for inhibitor testing, including confirmatory and unscheduled inhibitor tests. An unscheduled visit may be required to obtain samples to confirm a positive inhibitor test result.

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

[l] The predose sample collection for FIX activity, anti-rFIXFc antibody, and inhibitor testing are only required for subjects who received at least 1 dose of any product containing FIX, including commercially available rFIXFc or a blood product transfusion, prior to the dose for the baseline IR assessment.

[m] Volume and units of factor infused at Baseline IR must be calculated and recorded using the *actual* potency as described in the DHA and in Section 10.1.1 of the protocol. The dose of factor for the IR baseline is 50 IU/kg (Section 9.1.4). Samples for incremental recovery calculations to be taken when the subject is in a non-bleeding state and after at least a 72-hour washout. Blood samples will be taken predose within 30 minutes prior to the start of rFIXFc injection) and postdose 10 (±5) minutes after the end of the rFIXFc injection.

[n] 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 and Section 4.2.2.2). The subject's parent/legal guardian may provide consent in order to receive this testing at any time during the Treatment Period.

[o] Injection site inspection is to be performed after each injection of rFIXFc that the subject receives during a site visit.

[p] The subject/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 10.1.2). It is recommended that subjects/parents/caregivers enter dosing information immediately after an injection.

[q] It is recommended that the subject/parent/caregiver enter the response to a bleeding episode into the EPD as soon as possible after an injection (Section 10.2.3.2).

[r] AEs and SAEs are to be monitored and recorded starting from the time of signing informed consent.

[s] For subjects who are receiving breast milk, maternal concomitant medications will also be collected at the same timepoints 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 exposure day (ED) milestones (Section 4.2.2.2). Subjects on immune tolerance induction therapy (ITI) will participate in an ITI-specific schedule of interim visits (Section 4.2.4). Subjects requiring surgery will also participate in specialized visits (Section 4.2.3).

4.2.2.1. Schedule of Events: 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 events below.

Tests and Assessments	Interim Visits				ET/ EOS Visit	Safety Follow-Up[c]
	Episodic Regimen Visits every 12 (±2) weeks[a]		Prophylaxis Regimen Visits every 12 (±2) weeks[b]			
	Predose	Postdose	Predose	Postdose		
Physical Examination[d]					X	
Height					X	
Weight	X		X		X	
Vital Signs[e]	X	X	X	X	X	
Health Outcome[f]	X		X		X	
Hematology[g]	X		X		X	
Blood Chemistry[h]	X		X		X	
Nijmegen-Modified Bethesda Assay (Inhibitor Assay)[i,j]	X		X		X	
FIX Activity[k]			X	X		
Anti-rFIXFc Antibody[i]	X		X		X	
F9 Genotyping[j]	If needed					
Injection Site Inspection[l]		X		X		
Physician's Global Assessment of Response	X		X			
EPD Review, including rFIXFc Dosing Accountability[m]	<<<<<<<<<<<<<<<<<<< ONGOING >>>>>>>>>>>>>>>>>>					
rFIXFc Clinic Dosing[n]	X		X			

Tests and Assessments	Interim Visits				ET/ EOS Visit	Safety Follow-Up[c]
	Episodic Regimen Visits every 12 (±2) weeks[a]		Prophylaxis Regimen Visits every 12 (±2) weeks[b]			
	Predose	Postdose	Predose	Postdose		
Assessment of Response to Individual Bleeding Episodes in EPD by Subject/Parent/Caregiver[o]	<<<<<<<<<<<<<<<<<< ONGOING >>>>>>>>>>>>>>>>>					
Physician's Assessment of Response to Individual Bleeding Episodes Treated in Clinic[l]	<<<<<<<<<<<<<<<<<< ONGOING >>>>>>>>>>>>>>>>>					
Adverse Events[o,p]	<<<<ONGOING: Monitor and record at all visits; telephone call every month>>>>					
Serious Adverse Events[o,p]	<<<<ONGOING: Monitor and record at all visits; telephone call every month>>>>					
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; EOS = end of study; EPD = electronic patient diary; ET = early termination; F9 = target gene for hemophilia B; FIX = coagulation factor IX; HIV = human immunodeficiency virus; ICF = informed consent form; rFIXFc = recombinant coagulation factor IX 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 rFIXFc 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 14 (+7) days after the last dose of rFIXFc to monitor AEs, SAEs, and concomitant medications and procedures. This 14 day follow-up is not required if subjects end their participation in this study to enroll into another rFIXFc study.

[d] After screening, physical examination should be performed at least annually; more frequent physical examinations may be performed at the Investigator's discretion, according to their standard of care.

[e] Vital signs include blood pressure, pulse rate, respiratory rate, and temperature (°C). Postdose assessments following in-clinic injections should be taken approximately 10 minutes after the end of the rFIXFc injection.

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

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

[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] Washout prior to sample collection for inhibitor and anti-rFIXFc antibody testing should be at least 72 hours. Samples for anti-rFIXFc antibody testing will be collected at the same timepoint when any samples are collected for inhibitor testing, including confirmatory and unscheduled inhibitor tests. Testing for inhibitors and anti-rFIXFc antibodies will also be performed at specific ED milestones, see Section 4.2.2.2. An unscheduled visit may be required to obtain samples for repeat inhibitor and anti-rFIXFc antibody testing under this protocol to confirm a

positive inhibitor test result or if the inhibitor test at the ET/EOS Visit is not evaluable. In addition, if inhibitor development is suspected at any time during the study (e.g., the expected plasma FIX activity levels are not attained or if bleeding is not controlled with an expected dose), samples will be collected for inhibitor testing by the central laboratory and for anti-rFIXFc antibodies.

[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 any other 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] Samples for FIX activity will only be taken if the subject receives an rFIXFc injection during a site visit and is in a non-bleeding state, after a washout of at least 72 hours. Predose sample is to be collected within 30 minutes prior to the start of the rFIXFc injection; postdose sample is to be taken 10 (±5) minutes after the end of the rFIXFc injection.

[l] Injection site inspection is to be performed after each injection of rFIXFc that the subject receives during a site visit.

[m] The subject/ 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 10.1.2). It is recommended that subjects/parents/caregivers enter dosing information immediately after an injection.

[n] Clinic dosing applicable only if warranted.

[o] It is recommended that the subject/parent/caregiver enter the response to a bleeding episode into the EPD as soon as possible after an injection (Section 10.2.3.2). 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.

[p] AEs and SAEs are to be monitored and recorded starting from the time of signing informed consent.

[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.

Note: Additional unscheduled visits may be necessary during the study to test for inhibitors, test for recovery, repeat safety assessments, or repeat any blood sampling if required for study purposes or for local standard of care.

4.2.2.2. Schedule of Events: 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 and anti-rFIXFc drug antibody at the ED milestones shown below. One ED is defined as a 24 hour period in which a subject receives 1 or more doses of rFIXFc, with the time of the first injection of rFIXFc defined as the start of the ED. Testing for inhibitors and anti-rFIXFc antibody at these ED milestones 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.

Activities	Visits at			
	5 EDs (±2 EDs)	**10 EDs (10 to 15 EDs)**	**20 EDs (20 to 25 EDs)**	**50 EDs (50 to 55 EDs)**
Nijmegen-Modified Bethesda Assay (Inhibitor Assay)[a, b]	X	X	X	X
Anti-rFIXFc Antibody[a]	X	X	X	X
F9 Genotyping[b]	If needed			

ED = exposure day

[a] Washout prior to sample collection for the inhibitor and anti-rFIXFc antibody tests should be at least 72 hours. Samples for anti-rFIXFc antibody testing will be collected at the same timepoint when any samples are collected for inhibitor testing, including confirmatory and unscheduled inhibitor tests. An unscheduled visit may be required to obtain samples to confirm a positive inhibitor test result. In addition, if inhibitor development is suspected at any time during the study (e.g., the expected plasma factor IX activity levels are not attained or if bleeding is not controlled with an expected dose), samples will be collected for inhibitor testing by the central laboratory and for anti-rFIXFc antibody testing.

[b] 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 any other 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.

4.2.3. Schedule of Events: Surgery Visits

Tests and Assessments	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	X	
Hematology[f]		X[g]	X	X
Blood Chemistry[h]		X[g]	X	X
FIX Activity[i]	X[g]	X[g]	X	X
Nijmegen-Modified Bethesda Assay (Inhibitor Assay)[j, k]	X[g]	X[g]	X	X
rFIXFc Dosing[l]	X	X	X	X
Anti-rFIXFc Antibody[j, k]	X[g]	X[g]	X	X
EPD Review, including rFIXFc Dosing Accountability[m]	X	X	X	X
Investigator/Surgeon's Assessment of Response[n]		X	X	
AE/SAE Monitoring and Recording	<<<<ONGOING: Monitor and record at all visits>>>>			
Concomitant Therapy/ Procedures Recording	<<<<ONGOING: Monitor and record at all visits>>>>			

AE = adverse event; EOS = end of study; EPD = electronic patient diary; ET = early termination; FIX = coagulation factor IX; rFIXFc = recombinant coagulation factor IX 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 FIX activity and Nijmegen-modified Bethesda assay. For minor surgery, the Investigator is to be in contact with the subject or subject's parent/caregiver to determine when the subject should return to the regular pre-surgery regimen.

[c] Visit is required for major surgeries only.

[d] Visit is required for major surgeries only. This visit occurs when the Investigator determines the subject can return to the regular pre-surgery regimen and 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 ET/EOS Visit assessments (see Section 4.2.2.1) at least 2 weeks after surgery.

[e] Vital signs include temperature (°C), blood pressure, pulse rate, and respiratory rate. Postdose assessments following in-clinic injections should be taken approximately 10 minutes after the end of the rFIXFc injection.

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

[g] For minor surgeries, only to be performed if indicated by 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 determination of predose FIX activity levels will be collected prior to the dose of rFIXFc, given for the surgery, and FIX activity levels will be sampled 10 (±5) minutes after the end of the rFIXFc injection. For major surgeries, a repeat blood draw for FIX activity should be taken approximately 9 hours after the end of the injection but may alternatively follow local standard of care for determining when the next dose of rFIXFc should be administered. While hospitalized, blood will be drawn daily to be tested at the local laboratory for FIX activity so that monitoring of the subject can occur in real time.

[j] Washout prior to sample collection for inhibitor and anti-rFIXFc antibody testing should be at least 72 hours. If necessary, washout at postoperative visits can be shortened to at least 48 hours.

[k] Samples for anti-rFIXFc antibody testing will be collected at the same timepoint when any samples are collected for inhibitor testing, including confirmatory and unscheduled inhibitor tests. An unscheduled visit may be required to obtain samples to confirm a positive inhibitor test result.

[l] Clinic dosing is applicable only if warranted.

[m] Subjects who require postoperative treatment with rFIXFc at home for a bleeding episode will have their assessment of response to treatment recorded in the EPD. It is recommended that the subject/parent/caregiver enter the response to a bleeding episode into the EPD as soon as possible after an injection (Section 10.2.3.2).

[n] 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.

4.2.4. Schedule of Events: Immune Tolerance Induction Visits

The following schedule applies to subjects who are eligible for ITI, as described in Section 10.2.6.

Tests and Assessments	Pre-ITI Assessment (ITI Week 0)	ITI: Week 4 to Week 24 Visits every 4 (±2) weeks	ITI: Week 36 to EOT Visits every 12 (±2) weeks	Once Confirmed Negative Inhibitor: IR Assessments (add to an existing visit)[a]	ET/EOS Visit for ITI	Safety Follow-Up for ITI[b]
Informed Consent	X					
Physical Examination	X	X	X		X	
Weight (kg)	X	X	X		X	
Vital Signs[c]	X	X	X		X	
Hematology[d]	X	X[e]	X[e]		X	
Urinalysis	X	X	X		X	
Blood Chemistry[f]	X	X[g]	X[g]		X	
Nijmegen-Modified Bethesda Assay (Inhibitor Assay)[h,i]	X	X	X		X	
rFIXFc Dosing[j]	X	X	X	X	X	
FIX Activity	X[k]	X[k]	X[k]	X	X[k]	
Anti-rFIXFc Antibody[h, i]	X	X	X		X	
EPD Review, including rFIXFc Dosing Accountability[l]	X	X	X		X	
Injection Site Inspection[m]	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[n]	<<<<ONGOING: Monitor and record at all visits; telephone call every month>>>>					

AE = adverse event; DHA=Directions for Handling and Administration; EOS = end of study; EPD = electronic patient diary; EOT = end of treatment; ET = early termination; FIX = coagulation factor IX; ITI = immune tolerance induction; rFIXFc = recombinant coagulation factor IX Fc fusion protein; SAE = serious adverse event.

[a] The incremental recovery (IR) assessments will be performed once subjects have achieved 2 consecutive negative inhibitor tests, and could occur at any time during ITI treatment when these conditions are met; the IR assessment will be added to an existing visit for ITI treatment. Samples for IR assessments are to be taken when the subject is in a non-bleeding state, after at least a 72-hour washout. The volume and units of factor infused for these IR

assessments must be calculated using the actual potency as described in the DHA and in Section 10.1.1 of the protocol; the dose of rFIXFc for these IR assessments is 50 IU/kg. Blood samples will be taken predose within 30 minutes prior to the start of rFIXFc injection and postdose 10 (±5) minutes after the end of the rFIXFc injection. [redacted] For further details, see Section 10.2.6.4.

[b] A follow-up telephone or in person visit is required 14 (+7) days after the last dose of rFIXFc to monitor AEs, SAEs, and concomitant medications and procedures. The 14-day follow-up is not required if subjects end their participation in this study to enroll into another rFIXFc study.

[c] Vital signs include temperature (‡°C‡), blood pressure, pulse rate, and respiratory rate. Postdose assessments following in-clinic injections should be taken approximately 10 minutes after the end of the rFIXFc injection.

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

[e] Hematology will be performed every other visit during ITI, i.e., at Weeks 0, 8, 16, and 24, then every 12 weeks thereafter.

[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] Blood chemistry will be performed every other visit during ITI, i.e., at Weeks 0, 8, 16, and 24, then every 12 weeks thereafter.

[h] Washout prior to sample collection for inhibitor and anti-rFIXFc antibody testing should be at least 72 hours. The definitive Nijmegen assay for each timepoint must be performed by the central laboratory. Negative inhibitor titer must be confirmed with a second sample collected within 2 to 4 weeks of the first sample.

[i] Samples for anti-rFIXFc antibody testing will be collected at the same timepoint when any samples are collected for inhibitor testing, including confirmatory and unscheduled inhibitor tests. An unscheduled visit may be required to obtain samples for repeat inhibitor and anti-rFIXFc antibody testing under this protocol to confirm an inhibitor test result or if the inhibitor test at the ET/EOS Visit is not evaluable.

[j] Clinic dosing applicable only if warranted.

[k] At discretion of Investigator. Samples for FIX activity will be taken if the subject is in a non-bleeding state, after at least a 72-hour washout. Blood samples will be taken predose within 30 minutes prior to the start of rFIXFc injection and postdose 10 (±5) minutes after the end of the rFIXFc injection.

[l] The subject/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 10.1.2). It is recommended that subjects/parents/caregivers enter dosing information immediately after an injection.

[m] Injection site inspection is to be performed after each injection of rFIXFc that the subject receives during a site visit.

[n] For subjects who are receiving breast milk, maternal concomitant medications will also be collected at the same timepoints 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 will receive recombinant coagulation factor IX Fc fusion protein (rFIXFc; BIIB029) 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 clinical investigation of recombinant and human plasma-derived factor IX products [EMA (EMA/CHMP/BPWP/144552/2009) 2011] was followed in the development of this protocol.

5.1. Profile of Previous Experience

Hemophilia B (congenital coagulation factor IX [FIX] deficiency; Christmas disease) is an X-linked bleeding disorder that occurs predominantly in males, characterized by a deficiency of functional FIX. Hemophilia A and B are estimated to affect 460,000 people worldwide, with hemophilia B representing approximately 20% of those cases [Skinner 2012]. Hemophilia is a serious, life-threatening disorder. Individuals with severe hemophilia experience frequent and recurrent spontaneous or traumatic bleeding into the soft tissues, body cavities, and joints, leading to arthropathy, muscle contractures, and severe disability. A severe complication is central nervous system bleeding, resulting in death or disability [Ljung 2008]. Intracranial hemorrhage is one of the leading causes of bleeding death in individuals with hemophilia [Witmer 2011]. From an epidemiological perspective, severe hemophilia is defined as a FIX activity level of <1%; for the purpose of clinical studies, severe hemophilia is defined as a FIX activity level of ≤2% [Lambert 2007; Martinowitz 2012; Negrier 2011; Santagostino 2012].

5.1.1. Therapies for Hemophilia B

Clinical studies have led to the widespread adoption of prophylaxis as a major advance in treating hemophilia [Manco-Johnson 2007; Nilsson 1992; Nilsson 1970]. While these studies were predominantly conducted in subjects with hemophilia A, prophylaxis is currently considered standard of care in the developed world and is recommended by the World Federation of Hemophilia and the United States National Hemophilia Foundation's Medical and Scientific Advisory Council for both hemophilia A and B. Episodic treatment is associated with a high frequency of bleeding episodes, which vary in reported literature but can be approximately 20 bleeding episodes per year, whereas patients with hemophilia B who are treated prophylactically are reported to experience as few as 3 to 4 spontaneous bleeding episodes per year [Lambert 2007; Monahan 2010; Shapiro 2005]. Annual bleeding rates tend to be lower in children on primary prophylaxis [Manco-Johnson 2007] compared with older children or adults on secondary prophylaxis, who have joint damage that predisposes them to higher annual bleeding rates.

There is no currently available cure for hemophilia B. While innovations such as gene therapy are in development, current treatment focuses on factor replacement therapy with plasma-derived factor IX (pdFIX) or recombinant coagulation factor IX (rFIX) products. Currently available pdFIX and rFIX have similar efficacy and safety profiles. The rFIX concentrate, BeneFIX®, is not associated with the theoretical risk of blood-borne pathogen transmission [BeneFIX®

Prescribing Information 2011]. A limitation of rFIX is its short elimination half-life ($t_{½}$), with a mean of 18 to 22 hours and variably lower in vivo recovery compared with pdFIX products [BeneFIX® Prescribing Information 2011; Lambert 2007; Roth 2001].

5.1.2. rFIXFc

rFIXFc is a fully recombinant fusion protein consisting of a single molecule of human FIX covalently linked to the dimeric Fc domain of human immunoglobulin G1 (IgG1) with no intervening sequence. This type of construct has been termed a monomeric Fc fusion protein [Dumont 2006].

While the FIX moiety of rFIXFc retains FIX coagulation activity, the Fc component of rFIXFc binds with neonatal Fc receptor (FcRn), which is expressed on many adult cell types. The Fc domain is responsible for the long circulating $t_{½}$ of IgG1 through interaction with the FcRn [Roopenian and Akilesh 2007]. The same naturally occurring pathway similarly delays lysosomal degradation of immunoglobulins by recycling the protein back into circulation and is responsible for their long plasma $t_{½}$. rFIXFc is being developed as a treatment for hemophilia B that would have a longer circulating $t_{½}$ while maintaining the activity profile of FIX.

5.1.3. Summary of Preclinical Experience With rFIXFc

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

- Improved PK parameters (e.g., increased elimination $t_{½}$) were observed for rFIXFc in several animal species, and administered rFIXFc retained its functional activity while present in the circulation.
- Prolonged pharmacodynamics and efficacy were observed for rFIXFc in several animal species.
- Similar potency was found for rFIXFc and BeneFIX in an acute bleeding model.
- The toxicology program established that rFIXFc was well tolerated in 3 different species (rats, monkeys, and rabbits).
- The safety margin is 10-fold based on a comparison of no-observed-adverse-effect levels (1000 international units [IU]/kg) with the highest routine dose of 100 IU/kg used in clinical studies.

For further details regarding the preclinical studies conducted with rFIXFc, refer to the rFIXFc Investigator's Brochure.

5.1.4. Summary of Clinical Experience With rFIXFc

Three clinical studies, a Phase 1/2a study (Study SYN-FIXFc-07-001) and 2 Phase 3 studies (Study 998HB102 and 9HB02PED), have been completed. Two additional clinical studies, an extension study (Study 9HB01EXT) and this study in previously untreated patients or PUPs (Study 998HB303), are ongoing.

In the open-label, multicenter Phase 1/2a study (Study SYN-FIXFc-07-001), 14 previously treated patients (PTPs) ≥18 years of age with severe hemophilia B (defined as ≤2 IU/dL [≤2%] endogenous FIX) received a single injection of rFIXFc in escalating doses at 6 dose levels (1, 5, 12.5, 25, 50, and 100 IU/kg) and were evaluated for safety and PK. A single dose of rFIXFc was well tolerated at all dose levels administered in this study. None of the subjects developed inhibitors and there were no reports of drug-related serious adverse events (SAEs). Dose-linear PK of rFIXFc was demonstrated in the dose range of 12.5 to 100 IU/kg.

The Phase 3 study in adults and adolescents (Study 998HB102) was an open-label, multicenter study that evaluated the safety, PK, and efficacy of rFIXFc in 123 PTPs with severe hemophilia B (defined as ≤2 IU/dL [≤2%] endogenous FIX) ≥12 years of age, and with at least 100 prior EDs to a FIX product. The measured $t_{½}$ of rFIXFc was 82 hours, which is 2.43-fold longer than observed for BeneFIX (rFIX). rFIXFc was effective in the control of bleeding with >90% acute bleeding episodes controlled with a single injection. rFIXFc was effective in each of 2 routine prophylaxis regimens with >80% reduction in annualized bleeding rate (ABR) relative to episodic treatment. The median weekly dose during the last 6 months on study in the weekly prophylaxis arm was 40.7 IU/kg. The median dosing interval during the last 6 months on study in the individualized interval prophylaxis arm (dosed at 100 IU/kg) was 13.8 days. rFIXFc was effective when used for perioperative management, with 100% of major surgeries having excellent or good hemostasis.

The safety data from Study 998HB102 includes 123 subjects aged 12 years and older with severe hemophilia B, with 59 subjects having ≥50 EDs. Overall, the adverse event (AE) profile was generally consistent with that expected in patients with hemophilia B. No inhibitor development was observed in this clinical study. There were no severe allergic reactions or vascular thrombotic events. Adverse drug reactions (ADRs) were defined as AEs assessed by the Investigator as related or possibly related to the treatment with rFIXFc followed by medical review. The most common ADRs observed in the Phase 3 adult and adolescent study (incidence >1%) were headache and oral paresthesia. One serious ADR of obstructive uropathy was reported in a subject with hematuria who developed an obstructing clot in the urinary collecting system. The event resolved with hydration, and the subject continued prophylactic treatment with rFIXFc. The safety of rFIXFc was consistent across the patient population evaluated and there were no meaningful differences in safety profile by age, race, geography, body mass index, or co-morbidities such as hepatitis C virus or human immunodeficiency virus (HIV).

Phase 3 study 9HB02PED was an open-label, multicenter study of pediatric PTPs in which 30 subjects aged <12 years received at least 1 dose of rFIXFc. The pattern of AEs, including infections, reported during the study was typical of the population studied, and no unique safety issues were identified. The safety profile is consistent with that seen in the completed studies in

subjects 12 years and older. rFIXFc was effective for the control and prevention of bleeding when administered for routine prophylaxis. PK data showed that, consistent with the known impact of age on PK of coagulation factors, there appeared to be a decrease in incremental recovery (IR) and an increase in clearance in pediatric patients <12 years of age compared with adults and adolescents (Table 1). rFIXFc was also observed to have a prolonged $t_{½}$ and reduced clearance compared with other FIX products, consistent with results for subjects 12 years and older.

Phase 3 study 9HB01EXT is an ongoing open-label, multicenter extension study of the long-term safety and efficacy of rFIXFc in PTPs who completed other studies such as Study 998HB102 and 9HB02PED. As of 17 October 2014, the type and incidence of AEs observed in the study were generally similar to what is expected for the general adult and pediatric hemophilia population. The results from this study as of that date suggested that, in line with the parent studies (Studies 998HB102 and 9HB02PED), rFIXFc treatment during the extension study was well tolerated and effective for the prevention and treatment of bleeding and for routine prophylaxis using either a weekly regimen, an individualized regimen with injections approximately every 2 weeks, or a personalized regimen. Surgical data from 15 major surgeries in 8 subjects confirmed the efficacy of rFIXFc for perioperative management in major surgery.

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

Table 1: Comparison of rFIXFc PK Parameters by Age Category: Geometric Mean (95% Confidence Interval [CI])

Summary of FIX PK parameters by age category: geometric mean (95% CI) - noncompartmental methods - one-stage clotting assay
Pharmacokinetic Analysis Set

	Pediatric study (9HB02PED)		Phase 3 study (998HB102)	
PK parameter	<6 years (n=11)	6 to <12 years (n=13)	12 to 17 years (n=11)	>=18 years (n=109)
DNAUC (IU*h/dL per IU/kg)	22.71 (20.32, 25.38)	28.53 (24.47, 33.27)	29.50 (25.13, 34.63)	32.44 (30.95, 34.00)
t1/2 (h)	66.49 (55.86, 79.14)	70.34 (60.95, 81.17)	82.22 (72.30, 93.50)	76.36 (73.04, 79.83)
CL (mL/h/kg)	4.365 (3.901, 4.885)	3.505 (3.006, 4.087)	3.390 (2.888, 3.979)	3.083 (2.941, 3.231)
MRT (h)	83.65 (71.76, 97.51)	82.46 (72.65, 93.60)	93.46 (81.77, 106.81)	88.30 (84.72, 92.03)
Vss (mL/kg)	365.1 (316.2, 421.6)	289.0 (236.7, 352.9)	316.8 (267.4, 375.5)	272.2 (258.3, 286.8)
IR (IU/dL per IU/kg)	0.590 (0.515, 0.675)	0.717 (0.612, 0.841)	0.847 (0.677, 1.060)	0.964 (0.907, 1.025)

Note 1: For the purpose of this table, all treatment arms in the Phase 3 study have been grouped together.
2: CI = confidence interval; CL = clearance; DNAUC = dose-normalized area under the curve; IR = incremental recovery; MRT = mean residence time; t1/2 = terminal half-life; Vss = volume of distribution at steady state.

SOURCE: FACTOR9HB/SCS_SCE/INTERIM1/T-PK-BYSTUDY-NONCOMP.SAS DATE: 08APR2015

Source: rFIXFc Investigator's Brochure, V10.0, Table 3

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 FIX replacement therapies are limited by short $t_{½}$ requiring intravenous (IV) administration up to 3 times per week.

The purpose of this study is to investigate the safety and efficacy of rFIXFc in previously untreated patients (PUPs) in accordance with the EMA CHMP guideline on clinical investigation of recombinant and human plasma-derived factor IX products [EMA (EMA/CHMP/BPWP/144552/2009) 2011].

5.3. Rationale for Dose and Schedule Selection

Results of the Phase 1/2a study (Study SYN-FIXFc-07-001) evaluating the safety and PK of a single dose of rFIXFc suggested that rFIXFc is well tolerated when given as a single dose at doses ranging from 1 to 100 IU/kg. In the completed Phase 3 study (Study 998HB102), multiple doses between 20 and 100 IU/kg were generally well tolerated, with an AE profile generally consistent with that expected in patients with hemophilia B. No dose-limiting toxicity (DLT) has been identified to date in humans receiving a dose of rFIXFc up to 100 IU/kg.

The recommended starting prophylactic dose of rFIXFc in this study, approximately 50 IU/kg weekly, is based on the data from the Phase 1/2a and Phase 3 studies (including pediatric PK data from subjects <12 years of age) and knowledge of increased clearance of factor concentrates in children (Table 1). This dose is predicted to maintain trough levels >1% in 99% of pediatric subjects. Adjustments to the dose and interval of rFIXFc can be made in this study based on available PK data, subsequent FIX activity levels, level of physical activity, and bleeding pattern, in accordance with local standards of care for a prophylactic regimen.

The dose for treatment of bleeding episodes will target peak plasma FIX activity of approximately 30% to 100%, in accordance with local standards (see guidance provided in Appendix A), and taking into account lower rFIXFc recoveries observed in young children (Table 1). Subjects developing positive low titer inhibitors may continue on study at the same or higher dose per injection of rFIXFc at the discretion of the Investigator (see Section 10.2.6.2).

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

5.4. Potential Risks and Benefits

Refer to the current Investigator's Brochure for descriptions of the potential risks and benefits of rFIXFc.

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 rFIXFc in previously untreated subjects with severe hemophilia B.

6.1.2. Secondary Objectives

The secondary objectives of the study are as follows:

- To evaluate the efficacy of rFIXFc in the prevention and treatment of bleeding episodes in PUPs.
- To evaluate rFIXFc consumption for prevention and treatment of bleeding episodes in PUPs.

6.1.3. Exploratory Objectives

The exploratory objective of the study is to evaluate the effect of rFIXFc based on patient-reported outcomes and health resource utilization.

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 (spontaneous and traumatic) per subject
- the annualized number of spontaneous joint bleeding episodes per subject
- assessments of response to treatment with rFIXFc for bleeding episodes, using the 4-point bleeding response scale (Investigator assessment for bleeding episodes treated in the clinic; parent or caregiver assessment for all other bleeding episodes)
- the total number of EDs per subject per year
- total annualized rFIXFc consumption per subject for the prevention and treatment of bleeding episodes

- the number of injections and dose per injection of rFIXFc required to resolve a bleeding episode
- rFIXFc incremental recovery

6.2.3. Exploratory Endpoints

The exploratory endpoints include, but are not limited to:

- health outcomes

7. STUDY DESIGN

7.1. Study Overview

This is an open-label, single-arm, multicenter study evaluating the safety and efficacy of rFIXFc in previously untreated subjects with severe hemophilia B when used according to local standard of care. For the purpose of this study, a PUP is defined as a subject who has not had prior exposure to FIX concentrates, except for up to 3 injections of commercially available rFIXFc between 28 days prior to the first Screening Visit and the confirmation of eligibility. Following the confirmation of eligibility, administration of commercially available rFIXFc is no longer allowed and only rFIXFc labeled for study use is to be administered (henceforth, the latter supply will be described as rFIXFc study drug, to distinguish it from commercially available rFIXFc). Subjects with a documented plasma FIX activity of ≤2% may be enrolled on the basis of local laboratory results and may receive study drug after samples for factor IX activity level and inhibitors have been obtained for testing at the central laboratory. However, any such subject must be withdrawn if the central laboratory screening results indicate factor IX activity level >2% or a positive inhibitor. Baseline incremental recovery (IR) assessments described in Section 4.2.1 should be performed as soon as practicable once all eligibility criteria have been met and the subject has been enrolled. 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 or at an unscheduled visit.

Following confirmation of eligibility and enrollment, the Investigator has the option to treat a subject 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 20 previously untreated subjects are planned to complete the study after reaching at least 50 EDs with rFIXFc. One ED is defined as a 24-hour period in which a subject receives 1 or more doses of rFIXFc, with the time of the first injection of rFIXFc defined as the start of the ED.

Surgery is allowed during the study. See Section 10.2.7 for further instructions.

Immune tolerance induction (ITI) with rFIXFc is allowed during the study for those subjects developing, after exposure to rFIXFc study drug, a positive low titer inhibitor (≥0.60 and <5.00 Bethesda unit [BU]/mL) with bleeding episodes that cannot be adequately treated with rFIXFc, or a positive high titer inhibitor (≥5.00 BU/mL). See Section 10.2.6 for further instructions.

Because of the risk of allergic reactions with FIX concentrates, the first administration of rFIXFc (commercially available rFIXFc and/or study drug) must be performed under medical observation where proper medical care for allergic reactions could be provided. The first injection of rFIXFc study drug after the confirmation of eligibility must be administered by the Investigator or a qualified delegate. Thereafter, study drug may be administered by a parent/caregiver, a qualified medical professional under the direction of the Investigator, self-administered by older children, or given at the clinic. Study treatment may also be injected in the hospital, for example, during surgery or during hospitalization due to major bleeding.

See Figure 1 for a schematic of the study design and Section 4.2 for a description of each study visit and the required assessments. Section 10 describes the treatment of subjects during the study.

7.2. Study Specifics

7.2.1. Dose-Limiting Toxicity

No DLT has been identified to date in humans receiving doses of rFIXFc up to 100 IU/kg. Also, no DLTs were observed in the preclinical animal studies where repeat doses of up to 1000 IU/kg were evaluated. The dose for treatment of bleeding episodes will target peak plasma FIX activity of approximately 30% to 100%, in accordance with local standards (see guidance provided in Appendix A), and taking into account lower rFIXFc recoveries observed in young children (Table 1).

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. Each subject is considered to have completed their treatment period once they have reached at least 50 EDs to the study treatment, unless withdrawal from the study occurs, or the end of study is declared. EDs are defined as in Section 7.1.

See Figure 1 for a schematic of the study design.

7.3.1. Screening and Baseline Incremental Recovery Visits

Parents/legal guardians of subjects must be provided with the informed consent information 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 and subjects will come into the clinic to sign the informed consent/assent; then subjects will undergo screening.

Screening assessments to determine subject eligibility for the study will be collected within 8 weeks after the first Screening Visit (i.e., the first visit for any activity other than informed consent, which can occur prior to the subject's birth), see Section 4.2.1. As part of the screening process, the Investigator must have sufficient documentation of a subject's medical history to ensure previously untreated status.

If more than 8 weeks elapse and screening activities have not been completed, the inhibitor and factor IX activity 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), including factor IX activity ≤2% from the local laboratory (either at Screening or documented in the medical record) and collection of samples for inhibitor and factor IX activity testing at the central laboratory. If results from central laboratory testing of

the screening samples for inhibitor and factor IX activity subsequently reveal a factor IX activity level >2% or a positive inhibitor, the subject must be withdrawn.

The Baseline IR Visit assessments should be performed as soon as practicable once all eligibility criteria have been met and the subject has been enrolled. The Baseline IR Visit activities (Section 4.2.1) may be completed on the same day as Screening, or they may be completed as part of a separate visit or at an unscheduled visit. Baseline IR assessments must be performed when the subject is in a non-bleeding state, after at least a 72 hour washout. Eligible subjects will report to the study site for administration in the clinic of the Baseline IR Visit dose of 50 IU/kg by actual potency (see the Directions for Handling and Administration [DHA] and Section 10.1.1 of this protocol for further information on actual potency dosing). The dose will be delivered via a slow push IV injection over several minutes, at a rate of administration determined by the subject's comfort level. Subjects will be required to complete the assessments according to Section 4.2.1, including collection of FIX activity samples for the calculation of incremental recovery.

Bleeding episodes that occur prior to meeting all eligibility criteria should be treated with commercially available rFIXFc. If a subject requires more than 3 injections of commercially available rFIXFc prior to confirmation of eligibility, the subject will be considered a screen failure. In countries where rFIXFc is not yet commercially available, any bleeding episode that occurs prior to meeting eligibility criteria should be treated with another FIX concentrate and the subject will be considered a screen failure. After meeting eligibility criteria, all bleeding episodes should be treated with rFIXFc study drug. The Baseline IR Visit may be delayed until the subject is in a non-bleeding state and a 72-hour washout period may be safely performed.

7.3.2. Treatment

Following confirmation of eligibility and enrollment, the Investigator has the option to treat the subject with an episodic regimen for a period of time before initiating a prophylaxis regimen. The duration of the episodic period is at the Investigator’s discretion, in accordance with 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.

The date of transition from episodic treatment to a prophylaxis regimen must be captured on the electronic case report form (eCRF). The recommended starting prophylactic regimen is 50 IU/kg weekly, although adjustments to the dose and dosing interval of rFIXFc can be made based on available PK data, subsequent FIX activity levels, level of physical activity, and bleeding pattern, in accordance with local standards of care for a prophylactic regimen. Treatment will continue until the subject has reached at least 50 EDs to rFIXFc. Parents/caregivers, or children capable of self-injection, will be instructed on how to administer rFIXFc at home.

Following confirmation of eligibility and enrollment, subjects will report to the study site for 2 kinds of required visits during the Treatment Period:

- Scheduled Interim Visits: every 12 (±2) weeks after enrollment, by calendar date (Section 4.2.2.1).

- ED Milestone Visits: at 5 (±2) EDs, 10 to 15 EDs, 20 to 25 EDs, and 50 to 55 EDs (Section 4.2.2.2).

In addition to scheduled clinic visits, telephone calls with the subject's parents/caregivers are planned approximately once a month for study site staff to check on each subject's status.

Additional unscheduled 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 for local standard of care, 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 who develop inhibitors may be eligible for 24 months of Immune Tolerance Induction Therapy (ITI) (Section 4.2.4 and Section 10.2.6).

7.3.3. Post-Treatment Follow-Up

Subjects will perform the assessments of the Early Termination (ET)/End of Study (EOS) Visit after at least 50 EDs to rFIXFc has been achieved, if they have withdrawn from the study, or the end of study is declared. A Final Safety Follow-up Visit/Telephone Call will be conducted 14 (+7) days after the last dose of rFIXFc to assess the subject's status for AEs, SAEs, and concomitant treatments and procedures. It will be at the discretion of the Investigator to conduct the Final Safety Follow-up Visit by telephone or in person.

7.4. Study Stopping Rules

Bioverativ may terminate this study at any time, after informing Investigators. Investigators will be notified by the Sponsor 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 rFIX 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 rFIXFc. 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 when at least 20 subjects have reached at least 50 EDs with rFIXFc. Once this milestone has been achieved, all ongoing study subjects will be required to return to the study center for the Early Termination (ET)/End of Study (EOS) 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 timepoint specified in the individual eligibility criterion listed:

1. Ability of the subject or 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, and/or to provide assent, in accordance with national and local subject privacy regulations.

2. Male, age <18 years at the time of informed consent.

3. Weight ≥3.5 kg.

4. Severe hemophilia B defined as ≤2 IU/dL (≤2%) endogenous FIX documented with local laboratory results either in the medical record or as tested during the Screening Period. Any subject who is enrolled based on results of the local laboratory (from the medical record or at screening) must be withdrawn if the central laboratory screening results indicate a baseline FIX activity level >2% 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 timepoint specified in the individual criterion listed:

1. 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 (i.e., equal to or above lower limit of detection).

2. History of hypersensitivity reactions associated with any rFIXFc administration.

3. Exposure to blood components or injection with a FIX concentrate (including plasma derived) other than rFIXFc.

4. Injection with commercially available rFIXFc more than 28 days prior to Screening.

5. More than 3 injections of commercially available rFIXFc prior to confirmation of eligibility.

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

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 cells/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 steroids for treatment of asthma or management of acute allergic episodes or otherwise life-threatening episodes is allowed. Treatment in these circumstances should not exceed a 14-day duration.

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

An individual may be enrolled as a subject when the following minimum criteria have been met:

- Diagnosis of severe hemophilia B with factor IX activity ≤2% has been documented by the local laboratory.
  - Local laboratory data already present in the medical record are acceptable.
- Samples have been *drawn* for central laboratory testing for inhibitors and factor IX activity.
  - The results are not required at the time of enrollment.
  - If the results from central laboratory testing of the screening sample subsequently reveal a factor IX activity level >2% or a positive inhibitor, the subject will discontinue treatment and be withdrawn per Section 11.
- The individual 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 IX replacement products prior to enrollment.

9. ENROLLMENT AND REGISTRATION PROCEDURES

9.1. Screening and Baseline

The subject and/or subject's legally authorized representative (e.g., parent or legal guardian), must be provided with the informed consent/assent 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, and subject if applicable, will come into the clinic to sign the informed consent/assent.

Subjects (where applicable), and/or parents/legal guardians, must provide consent/assent before any screening assessments are performed (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 Voice/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 (i.e., 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.

Refer to the Study Reference Manual for the IXRS User Manual.

9.1.1. Screening Assessments

Screening assessments should be completed within a total of 8 weeks after the first Screening Visit (i.e., the first visit for any activity other than informed consent, which can occur prior to the subject's birth) (Section 4.2.1). If more than 8 weeks have elapsed, and the subject has not been enrolled in the study, some screening assessments will need to be repeated (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. 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 14.6).

If the subject meets all study entry criteria based on the minimum criteria for enrollment, the subject can be enrolled and begin treatment with rFIXFc study drug. If results from central laboratory testing of the screening laboratory sample subsequently reveal factor IX activity level >2% or a positive inhibitor, the subject will discontinue treatment and be withdrawn per Section 11.

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.

9.1.2. Bleeding Episodes Prior to Meeting All Eligibility Criteria

In the event that a subject sustains a bleeding episode that requires treatment prior to meeting all eligibility criteria, the subject's parent/legal guardian should contact the site immediately. Bleeding episodes that occur prior to the subject meeting all eligibility criteria may be treated with up to 3 doses of commercially available rFIXFc using Appendix A as a guideline. If the subject receives more than 3 injections of commercially available rFIXFc during the period from 28 days prior to Screening to the confirmation of eligibility, the subject will be considered a screen failure. If rFIXFc is not commercially available, the subject should be treated with another FIX concentrate and will be considered a screen failure.

Any bleeding episode that occurs after the subject has met all eligibility criteria should be treated with rFIXFc study drug.

9.1.3. 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 rFIXFc 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 confirmation of eligibility and enrollment, the subject should be treated only with rFIXFc study drug. Subjects treated with another FIX concentrate must permanently discontinue study treatment and be withdrawn from the study, although exceptions are allowed for 1 emergency or accidental use (Section 11).

Subjects or their parent/caregiver must be issued with an electronic patient diary (EPD) once eligibility has been confirmed and the subject has been enrolled (see Section 10.1.2 for further details regarding information to be recorded into the EPD).

9.1.4. Baseline Incremental Recovery

Baseline IR assessments described in Section 4.2.1 should be performed as soon as practicable once all eligibility criteria have been met and the subject has been enrolled. 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 or at an unscheduled visit. They must be performed when the subject is in a non-bleeding state and after at least a 72 hour washout. The Baseline IR Visit may be delayed until the subject is in a non-bleeding state.

The sample for predose FIX activity does not have to be collected if the subject has not received any dose of any product containing FIX (including commercially available rFIXFc or a blood product transfusion) prior to the dose for the baseline IR assessment.

For the Baseline IR measurement, a dose of 50 IU/kg will be given in the clinic as an IV injection. The *actual* potency of rFIXFc must be used to calculate the units and volume of rFIXFc infused for the Baseline IR Visit dose (see the DHA and Section 10.1.1 of this protocol).

For the baseline IR assessment, blood samples will be taken predose within 30 minutes prior to the start of the injection and postdose at 10 (±5) minutes after the end of the rFIXFc injection for assessment of IR, measured by the one-stage aPTT clotting 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 rFIXFc and the collection of the samples.

9.2. Registration of Subjects

At the Screening Visit, an IXRS will be used to assign each subject a unique 6-digit subject identification number (Section 9.1).

Refer to the Study Reference Manual for details of registration.

9.3. Blinding Procedures

Not applicable. This is an open-label study.

10. TREATMENT OF SUBJECTS

The Sponsor will provide rFIXFc to the study sites via its designated distributors.

10.1. Study Treatment Schedule and Administration

During the Treatment Period, subjects will be treated with rFIXFc according to the schedules 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.

Additional visits may be necessary during the study to test for inhibitors, 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 visit assessments performed throughout the study on the eCRF.

Subjects requiring surgery will also be followed via specialized visits (Section 4.2.3).

Instructions for preparation and administration of rFIXFc are provided in the DHA and the Information for Patients. Dosing will be calculated as in the DHA and summarized in Section 10.1.1 of this protocol. See Section 12 for specifics on the preparation, storage, handling, disposal, and accountability of study treatment.

rFIXFc 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 FIX concentrates, the first administration of rFIXFc (commercially available rFIXFc and/or study drug) must be performed under medical observation where proper medical care for allergic reactions could be provided. The first injection of rFIXFc study drug after the confirmation of eligibility must be administered by the Investigator or a qualified delegate. Subjects and parents/caregivers will be instructed to administer subsequent rFIXFc doses at home, or to have them administered by a qualified medical professional under the direction of the Investigator or at the clinic.

Treatment will continue until the subject has reached at least 50 EDs to rFIXFc, discontinues, completes ITI, or the end of study is declared. The end of the study for all subjects is described in Section 7.5.

10.1.1. Dosing Based on Actual Potency or Nominal Strength

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 and Nominal Doses

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

- ***Dosing with partial vials (Actual Potency dosing)*, including the dose used for the calculation of Baseline IR, the dose used for IR assessments during ITI**, and any other doses where the Investigator decides to use a partial vial. The ***actual*** potency shown on the vial must be used to calculate the units of rFIXFc and the volume to inject. Actual potency dosing is required for the dose of 50 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*. 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 with whole vials,* including doses used for prophylactic treatment, treatment of bleeding episodes, surgery, and the assessment of FIX activity at interim visits.** The ***nominal*** strength must be used for calculations. Whole vials will be used to achieve the target dose, rounded as described in the DHA manual. 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 and the Sponsor prior to use).

10.1.2. Information to be Recorded for Treatment

All rFIXFc injections administered during a study site visit must be recorded in the eCRF. An injection administered during a site 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 at the study site, including doses for surgery, must be recorded in the eCRF.

All rFIXFc injections administered at home by the subject or the parent/caregiver or at locations other than the study site must be entered into the EPD.

The subject or 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 subjects or parents/caregivers enter dosing information immediately after an injection.

The study sites and Clinical Monitors will ensure that there is consistency in dosing information between the subject's medical record, IXRS, source documents, EPD, and eCRFs.

10.2. Treatment

10.2.1. Interim Visits

10.2.2. Assessment of FIX Activity During Interim Visits

If an injection is administered during an Interim Visit while a subject is on a prophylactic dosing regimen, predose and postdose samples will also be taken to assess the need for a possible dose adjustment. Samples should be taken when the subject is in a non-bleeding state and after at least a 72 hour washout.

The subject's current prophylactic dose of rFIXFc may be used for FIX activity assessments at Interim Visits. (For additional details on dosing, see the DHA, as well as Section 10.1.1 of this protocol).

rFIXFc 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 10 (±5) minutes after the end of the rFIXFc injection, measured by the one-stage aPTT clotting 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 rFIXFc and the collection of the samples.

Assessment of FIX activity during ITI is discussed separately in Section 10.2.6.4.

10.2.2.1. Episodic Treatment (Optional)

Once eligibility has been confirmed and the subject has been enrolled, the Investigator has the option to treat the subject episodically, until a prophylactic regimen is initiated. Dosing will be determined by the Investigator using Appendix A as a guideline. 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 eCRF.

10.2.2.2. Prophylaxis Treatment

It is anticipated that subjects will begin a prophylaxis regimen after confirmation of eligibility, prior to or immediately following the occurrence of a third hemarthrosis (joint bleed). The recommended initial prophylactic regimen is 50 IU/kg weekly. Adjustments to the dose and dosing interval can be made based upon available incremental recovery data, subsequent FIX activity levels, level of physical activity, and bleeding pattern, in accordance with local standards of care for a prophylactic regimen.

Subjects and parents/caregivers will be instructed to administer rFIXFc at home or to have it administered by a qualified professional under the direction of the Investigator or given at the clinic. Treatment will continue until the subject has reached at least 50 EDs to rFIXFc study drug or the end of study is declared, see Section 7.5).

10.2.3. Treatment of Bleeding Episodes

10.2.3.1. Definitions of 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 EPD will serve as the primary source document for bleeding episodes while on study.

Spontaneous bleeding episodes: Bleeding episodes should be classified as spontaneous if a parent/caregiver/subject 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/subject 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.

10.2.3.2. Information to be Recorded for Bleeding Episodes

Subjects or their parent/caregiver must be issued with an EPD once eligibility has been confirmed and they have been enrolled; from that point forward, all data regarding bleeding episodes and injections administered for a bleeding episode for doses administered at the subject's home or at locations other than the study site must be entered into the EPD. The incidence of bleeding in this study will be obtained from EPDs, eCRFs, and medical records. If a subject has enrolled in the study, information from medical records on dosing and bleeding episodes treated with commercially available rFIXFc prior to the subject being issued with an EPD should be recorded in the eCRF, according to the eCRF Completion Guidelines.

It is recommended that subjects or parents/caregivers enter bleeding episode information into the EPD immediately after an injection.

The Investigators and Clinical Monitors will ensure that there is consistency in bleeding episode data 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 subject/parent/caregiver will be reminded about timely EPD completion and the Investigator will verify whether or not a bleeding episode has occurred, and was "spontaneous" or "traumatic" (Section 10.2.3.1).

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 (e.g., spontaneous, 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

10.2.3.3. Determination of the rFIXFc Dose to Treat a Bleeding Episode

The dose of rFIXFc 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.

10.2.3.4. Procedure to Treat the Bleeding Episode

After meeting eligibility criteria, all bleeding episodes should be treated with rFIXFc study drug. Dosing calculations should be performed as described in the DHA and summarized in Section 10.1.1 of this protocol.

Subjects and their parents/caregivers should be instructed to treat at the first sign of a bleeding episode and with a single dose of rFIXFc. Most bleeding episodes should resolve with a single dose of rFIXFc. See Section 10.2.3.4 and Appendix A for rFIXFc dosing guidance.

- If the bleeding episode resolves with a single IV dose of rFIXFc, the subject will return to the schedule of dosing used prior to the bleeding episode.
- If the bleeding episode does not resolve within 48 hours with the single IV dose of rFIXFc, the subject's parents/caregivers should contact the Investigator for advice. Administration of a second dose of rFIXFc 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 rFIXFc dosing schedule used prior to the bleeding episode.
- If the bleeding episode does not resolve with 2 doses (initial and follow-up treatments) of rFIXFc, the subject's parents/caregivers should contact the Investigator for advice. A third dose of rFIXFc will be administered within 48 hours after the administration of the second dose of rFIXFc. 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 rFIXFc 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 rFIXFc, the Investigator should consult with the Medical Monitor to determine if the subject should be withdrawn from the study. See Section 11.

10.2.3.5. Dose and/or Interval Modification Following Bleeding Episodes

See Section 10.2.3.5 for guidance on dose and/or interval modification.

10.2.4. Inhibitor Testing

Subjects will be tested for inhibitor and anti-rFIXFc antibody formation at each clinic visit. Samples for anti-rFIXFc antibody testing (see Section 10.2.5) will be collected at the same timepoint when any samples are collected for inhibitor testing, including confirmatory and

unscheduled inhibitor tests, tests for suspected inhibitor development, and as required before and after surgery. Washout prior to sample collection for inhibitor testing should be at least 72 hours. Testing for inhibitors must also be conducted at ED Milestone Visits, as described in Section 4.2.2.2. If these do not align with a scheduled study visit, an additional visit must be scheduled to complete this testing. Additional unscheduled testing for inhibitors may be performed if required by local standards of care, and inhibitor test results must be recorded on the eCRF.

Testing for inhibitors must also be performed 2 to 4 weeks prior to elective major surgery, preoperatively, postoperatively, and at the Last Postoperative Visit (see Section 4.2.3). For minor surgeries, testing for inhibitors will only be performed if indicated by the nature of the procedure, according to local standard of care.

A valid inhibitor test result is required from the ET/EOS Visit. An unscheduled visit may be required to repeat inhibitor testing under this protocol if the ET/EOS Visit inhibitor test is not evaluable, or to obtain samples to confirm a positive inhibitor test result.

In addition, if inhibitor development is suspected at any time during the study (e.g., the expected plasma FIX 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.

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 2 to 4 weeks following the original sample. Both tests must be performed by the central laboratory using the Nijmegen-modified Bethesda assay.

A low titer inhibitor is defined as a positive inhibitor test with a result of ≥0.60 and <5.00 BU/mL. A 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 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. Anti-rFIXFc Antibody Testing

At the same timepoints that samples are drawn for inhibitor testing (see Section 10.2.4), blood samples will be collected for anti-rFIXFc antibody [redacted] testing, including back up and archiving samples. Anti-rFIXFc antibody samples will be collected when inhibitor samples are collected for confirmatory and unscheduled inhibitor tests, tests for suspected inhibitor development, and as required before and after surgery. Samples may also be collected and archived at the time of any clinical event deemed relevant to inhibitor or anti-rFIXFc antibody testing. [redacted]

10.2.6. Immune Tolerance Induction

10.2.6.1. Inhibitor Subgroup

Subjects developing positive inhibitors following exposure to rFIXFc study drug will be assigned to the Inhibitor Subgroup. Subjects with confirmed or suspected inhibitors may receive bypassing agents. For more information on the use of bypassing agents see Section 10.2.6.4.

10.2.6.2. Low Titer Inhibitors

Subjects developing positive low titer inhibitors will continue on study at the same or higher dose per injection of rFIXFc at the discretion of the Investigator. These subjects will continue with the schedule of assessments in Section 4.2.2.1 and Section 4.2.2.2.

If the Investigator determines that bleeding is no longer reliably controlled with rFIXFc in a subject with a positive low titer inhibitor, the subject will be eligible for ITI (see Section 10.2.6.4). If the subject declines to undergo or continue ITI, they will be withdrawn from the study. Subjects undergoing an ITI regimen will follow the schedule of assessments in Section 4.2.4, in addition to any other ITI regimen-specific assessments required.

10.2.6.3. High Titer Inhibitors

Subjects developing positive high titer inhibitors will be eligible for ITI (see Section 10.2.6.4). If the subject declines to undergo or continue ITI, they will be withdrawn from the study. Subjects undergoing an ITI regimen will follow the schedule of assessments in Section 4.2.4, in addition to any other ITI regimen-specific assessments required.

10.2.6.4. 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 FIX to overwhelm the inhibitor by antigen excess. In subjects with high-titer inhibitors, bleeding may be treated with bypassing agents, which can bypass FIX inhibition. During the study, the Investigator will determine if increased doses of replacement FIX 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 FIX 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 rFIXFc 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.

10.2.6.5. Immune Tolerance Induction Therapy

Subjects who develop a positive low titer inhibitor that cannot be adequately managed with rFIXFc or who develop a positive high titer inhibitor (≥5.00 BU/mL) will be eligible to undergo ITI with rFIXFc. The Medical Monitor will work with the Investigator to ascertain an established ITI regimen of the Investigator's choice, using rFIXFc. The ITI regimen plan must be approved for each subject by Bioverativ's Study Medical Director. The ITI regimen can be modified during this study, but requires re-approval by Bioverativ's Study Medical Director.

In order to use rFIXFc in an ITI regimen plan, the subject or their parents/legal guardians must sign a separate consent and the subject must provide assent, as applicable, at or prior to the Pre-ITI Assessment Visit (ITI Week 0).

rFIXFc will be provided for a period of up to 24 months under an ITI protocol. The 24-month duration is based on data from the North American Immune Tolerance Registry, which demonstrated a median time to completion of therapy of 11.6 months [Dimichele 2009].

- The ITI regimen must provide adequate oversight to detect and manage potential complications associated with ITI in FIX-deficient subjects, including nephrotic syndrome and severe allergic reactions. Please see the Schedule of Events for the ITI Visits (Section 4.2.4) for procedures to be performed during the ITI treatment period.

[redacted]

[redacted]

IR calculations will be performed on results obtained from the predose and postdose FIX activity samples collected under the following conditions for both the initial and the confirmatory IR assessment:

- The subject must be in a non-bleeding state, after at least a 72-hour washout.
- At the clinic, a predose FIX activity sample will be collected within 30 minutes prior to the start of injection.
- An rFIXFc dose of 50 IU/kg will be given. The actual potency shown on the vial must be used to calculate the units of rFIXFc and the volume to inject, as described in Section 10.1.1.
- A postdose FIX activity sample will be collected 10 (±5) minutes after the end of the rFIXFc injection.

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

[redacted]

If the criteria for success have not been met, the subject may remain on ITI at the discretion of the Investigator, up to a total duration of ITI of 24 months, at which point the subject will be required to perform the assessments of the ET/EOS Visit for ITI (see Section 4.2.4).

Subjects who choose to discontinue ITI prior to meeting the criteria for successful immune tolerance will perform the assessments of the ET/EOS Visit for ITI (see Section 4.2.4) and then be withdrawn from the study.

10.2.6.6. Treatment of Bleeding Episodes During Immune Tolerance Induction Therapy

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

Use of immunomodulatory agents during ITI is allowed at the Investigator's discretion.

10.2.7. Surgery

Minor surgery is allowed at any time during the study. Major surgery will only be allowed in the study after the subject has had at least 3 EDs to rFIXFc without safety concerns. If a subject needs to undergo major surgery prior to 3 EDs, 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 rFIXFc 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 rFIXFc 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.

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, port placement or removal, incision and drainage of abscess, or simple excisions).

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 FIX activity levels and inhibitor formation will be collected prior to the dose of rFIXFc given for the surgery, and FIX recovery levels will be sampled 10 (±5) minutes after the end of the rFIXFc injection.

For major surgeries, a repeat blood draw for FIX activity should be taken approximately 9 hours after the end of the injection, but may alternatively follow local standard of care for determining when the next dose of rFIXFc should be administered. While hospitalized, blood will be drawn daily to be tested at the local laboratory for FIX activity so that monitoring of the subject can occur in real time.

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

Bleeding caused directly by surgery should not be reported, although undesired or unexpected bleeding during or after surgery should be recorded on the eCRF.

10.2.7.1. Surgical Period

For all elective surgeries, subjects will begin the surgical period with their first dose of rFIXFc given for the surgery (i.e., the pre-surgery dose). This is the preoperative period of the surgery. 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 time when the subject can return to their regular pre-surgery regimen, as judged by the Investigator/Surgeon.

See Section 4.2.3 for the surgery visit schedule. Postoperative visits are only required for major surgeries. For minor surgeries, the Investigator will contact the subject/subject's caregiver after the day of surgery to determine when the subject returns to their regular pre-surgery regimen. For minor surgeries, pre-surgery assessments of FIX activity, inhibitor, and anti-rFIXFc 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. The Investigator or Surgeon's assessment of response is conducted on the day of surgery for minor surgeries; for major surgeries, the assessment occurs 24 hours after surgery and at the Postoperative Visit (1 to 2 weeks after surgery).

10.2.7.2. Dosing During Surgery

For subjects who require emergent or elective surgery during the study period, the target FIX 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 rFIXFc during the surgery may be discussed between the Investigator and Medical Monitor taking factors such as standard doses of FIX for the type of surgery, the clinical status of the subject, and incremental recovery data for the subject into consideration.

10.2.7.3. Rehabilitation Period

If surgery-related dosing is to be continued during postoperative rehabilitation, the dose of rFIXFc will be adjusted to achieve a trough at a sufficient level to maintain hemostasis, including during physical therapy.

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

10.3. Treatment Precautions

Epinephrine for subcutaneous injection, antihistamine for IV injection, and any other medications and resuscitation equipment for the emergency management of anaphylactic reactions must be available in the room where the subject's first injection of rFIXFc (commercially available rFIXFc and/or study drug) is being performed. The subject's first injection of rFIXFc study drug after the confirmation of eligibility must be performed by the Investigator or by qualified medical personnel identified by the Investigator. In addition, the subjects or parents/caregivers (as appropriate) 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 7.3.2.

10.5. Non-Medical Treatment With rFIXFc

During the study, subjects' parents/caregivers or subjects may attend training sessions on administration of rFIXFc. Administration of rFIXFc for training purposes will be considered nonmedical treatment. Such training is permitted and must be recorded in the EPD. However, subject/parent/caregiver administration with the first dose of rFIXFc 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

Any subject who reaches at least 50 EDs of rFIXFc, is considered to have completed treatment.

For subjects undergoing ITI with rFIXFc, the end of treatment occurs when:

1. The subject has achieved successful immune tolerance as defined in Section 10.2.6 .

OR

2. The subject has completed 24 months on an ITI regimen without achieving successful immune tolerance.

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/EOS visit.

The Final Safety Follow-up Visit (by telephone or in person) will be conducted within 14 (+7) days after the last dose of rFIXFc to assess the subject's status, collect AEs and/or SAEs, collect 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 Section 10.1.1 of this protocol.

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 or caregivers will administer (or older children will self-administer) rFIXFc 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. Refusal of the mother to provide consent for collection of her concomitant medication data will not affect the eligibility of the subject to participate in the study. The list of disallowed concomitant medications below does not apply to the mother's medications.

Subjects (and their parents/caregivers) should be instructed that the subject not start taking any new medications, including nonprescription drugs and herbal preparations, unless they have received permission from the Investigator.

Allowed Concomitant Therapy

Therapy considered necessary for the subject's welfare, including routine immunizations, may be given at the discretion of the Investigator. Immunomodulatory therapies are allowed at the Investigator's discretion if administered as part of an approved ITI regimen. Bypassing agents (e.g., aPCC [FEIBA], rFVIIa [NovoSeven]) are allowed in subjects with confirmed or suspected inhibitors as outlined in Section 10.2.6.4. 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.

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 steroids for treatment of asthma or management of acute allergic episodes or otherwise life-threatening episodes is allowed. Treatment in these circumstances should not exceed a 14-day duration.
- any other FIX 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 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 rFIXFc is proven to be beneficial, all regulatory requirements regarding poststudy 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:

- The subject is found to have FIX activity >2% or a positive inhibitor based on central laboratory results from samples collected during the screening period
- Development of a Grade 2 or greater allergic drug reaction in association with the administration of rFIXFc, as defined below 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
- Development of a positive inhibitor as defined in Section 10.2.4, either a low titer inhibitor with bleeding that is no longer reliably controlled with rFIXFc or a high titer inhibitor, and opting not to undergo or continue ITI
- Use of FIX products other than rFIXFc (exception allowed for 1 emergency or accidental use); a further exception is the use of activated prothrombin complex concentrate for subjects developing inhibitors (see Section 10.2.6.6)
- Development of any condition that precludes subjects from complying with the study procedures
- A medical emergency that necessitates discontinuation of treatment
- Judgment of the Investigator: a subject may have treatment permanently discontinued if, in the opinion of the Investigator, it is not in the subject's best interest to continue with the study treatment
- The parent/legal guardian can withdraw the subject from the study, or the subject can withdraw from the study, at will at any time
- At the discretion of the Investigator or Sponsor for 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 rFIXFc, as determined by the Investigator, a decision will be made with the Sponsor whether to continue the subject in the study.

If the decision is made to withdraw the subject from the study, the ET/EOS Visit assessments will be performed as described in Section 4.2.

12. STUDY TREATMENT MANAGEMENT

Refer to the Study Reference Manual for full details regarding rFIXFc. Study site staff should refer to the DHA located in the Study Reference Manual for specific instructions on the handling, preparation, administration, and disposal of rFIXFc. **The DHA supersedes all other references (e.g., Investigator's Brochure and protocol).**

The study treatment, rFIXFc, 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. rFIXFc (BIIB029)

rFIXFc is supplied in a kit that contains several components: a vial of lyophilized drug, a prefilled diluent syringe, a vial adapter, and a winged infusion set (see DHA for further details). The lyophilized powder is in a clear glass vial containing 250, 500, 1000, or 2000 IU of rFIXFc (nominal strengths). The drug product is reconstituted with a prefilled diluent syringe containing [redacted] sodium chloride. After reconstitution of the lyophilized drug product, the concentrations of excipients for the 250, 500, 1000, and 2000 IU/vial strengths are [redacted] L-histidine, [redacted] sucrose, [redacted] mannitol, [redacted] polysorbate 20, and [redacted] sodium chloride.

The label will comply with local labeling requirements.

12.1.1. rFIXFc Preparation

At the first visit when study drug 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 rFIXFc 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 rFIXFc 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. rFIXFc Storage at Site

The study treatment, rFIXFc, must be stored in a secure location. The rFIXFc 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. rFIXFc Handling and Disposal

The Investigator must return all used and unused kits of rFIXFc 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 or designee, by providing, in writing, the destruction policy or details of the method of destruction. After such destruction, Bioverativ or designee 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. rFIXFc 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 or lost. 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 ACTIVITY 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 rFIXFc:

- Recording of bleeding episodes in the eCRF for doses administered at the study site by the Surgeon/Investigator; recording of bleeding episodes in the EPD for doses administered at home by the parents/legal guardians/subjects or at locations other than the study site.
- Assessment of response to bleeding episodes using the 4-point scale by the Investigator for individual bleeding episodes treated at the study site; assessment of all other bleeding episodes in the EPD by the parents/legal guardians/subjects. See Appendix B.
- Physician's global assessment of the subject's response to their treatment regimen using the 4-point scale. See Appendix C.

13.2. Laboratory Efficacy Assessments

Not applicable.

13.3. Pharmacokinetic Assessments

Pre- and postdose samples are to be collected at the Baseline IR Visit for the calculation of incremental recovery (the Screening sample may replace the predose Baseline IR sample if the subject has not received any dose of any FIX-containing product prior to the dose for the baseline IR assessment, see Section 9.1.4). In addition, samples for measurement of FIX activity levels are to be collected at all Interim Visits during the prophylaxis regimen when rFIXFc is administered in the clinic (see Section 7.3.2). For subjects undergoing ITI who have a confirmed negative inhibitor, samples are to be collected for the calculation of IR (see Section 4.2.4 and Section 10.2.6.4 for details). Sample collection for FIX activity assessments at other timepoints during ITI treatment is at the discretion of the Investigator. Samples collected at the Baseline IR, interim visits, and if applicable during ITI treatment will be analyzed for FIX 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 4.2.3. While hospitalized, blood will be drawn daily to be tested at the local laboratory for FIX activity so that monitoring of the subject can occur in real time.

See Section 4.2 for the timing of assessments.

13.4. Pharmacodynamic Assessments

Not applicable.

13.5. Additional Assessments

13.5.1. Factor 9 Genotyping (Optional)

For subjects whose genotype is not known, with consent from the subject's parents/legal guardians, a sample will be drawn for analysis at the predose Baseline IR Visit (or at a subsequent visit if blood volume is limiting at that visit, see Section 4.2.1, Section 4.2.2.1, and Section 4.2.2.2). The subject's parent/legal guardian may provide consent in order to receive this testing at any time during the Treatment Period. 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.

Genotyping will also be requested for subjects whose genotype is not known and who develop an inhibitor during the study.

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].

There is 1 target gene for hemophilia B. The name of the target gene is F9.

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

[redacted]

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

13.5.2. Health Outcomes Related to Hemophilia

Assessments of health outcomes related to hemophilia will 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/guardian or caregiver (demographic data for caregivers may be collected at the Screening Visit)
- primary method of administering rFIXFc

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 assess the safety profile of rFIXFc:

- 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 assess the safety profile of rFIXFc. 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. Sample volume restrictions are described in Section 14.6.

- 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
- urinalysis

See Section 4.2 for the timing of assessments.

14.3. rFIXFc-Specific Safety Assessments

The following assessment will be performed to determine the safety of rFIXFc:

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

14.4. Additional Assessments

The following exploratory assessment will be performed:

- anti-rFIXFc antibodies (detection, titer, and specificity)

14.5. Archive Samples

14.5.1. Archive Plasma Samples

Plasma samples from each subject obtained at each sampling timepoint for inhibitor and anti-rFIXFc antibody testing 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:

- testing for coagulation parameters
- lupus anticoagulant
- additional testing (including testing for anti-rFIXFc antibody) 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
- testing for immunology (including testing for anti-rFIXFc antibody) 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.

No samples will be used for genetic analyses except F9 genotype retesting, if required(see Section 13.5.1 for further details).

14.6. Sample Volumes

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]. Examples of recommended blood draw volume limits per the European Commission guidance are provided in Table 2. Alternatively, individual investigators may choose to collect all 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.

Local and/or regional guidelines regarding blood draw volumes may also apply.

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. Study site staff will monitor and record AEs and SAEs that occur between clinic visits when subjects return for clinic visits and during monthly telephone calls. 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 parents/legal guardians 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.

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

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

Bleeding episodes in this patient population are not considered 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). Bleeding episodes that meet a serious criterion (Section 15.1.2) should be reported as an SAE. Bleeding episodes will be recorded as described in Section 10.2.3.2 and Section 13.1.

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 signing of the ICF, but before administration of rFIXFc (commercially available rFIXFc or study drug). A serious pretreatment event is to be reported 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); such an event will be recorded in the eCRF.

Any serious adverse event that occurs after the first dose of commercially available rFIXFc but prior to signing of the ICF should be reported as a post-marketing event; such an event will not be considered a serious pretreatment event and will not be recorded in the eCRF.

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, 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 reasonable 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 by Bioverativ according to the Investigator's Brochure for rFIXFc.

15.3. Monitoring and Recording Events

15.3.1. Adverse Events

Any AE experienced by the subject between the time of signing of the ICF and the Safety Follow-up Visit 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.

Any adverse event that occurs after the first dose of commercially available rFIXFc but prior to signing of the ICF should be reported as a post-marketing event; such an event will not be recorded in the eCRF.

15.3.2. Serious Adverse Events

Any SAE experienced by the subject between signing of the ICF and the end-of-study Safety Follow-up Visit is to be reported on an SAE Form and recorded in the eCRF, 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 also must be reported within 24 hours of the study site staff becoming aware of the SAE.

Subjects will be followed for all SAEs until the Safety Follow-Up Visit, which will be 14 (+7) days after the last dose. Thereafter, the event should be reported to Quintiles Pharmacovigilance only if the Investigator considers the SAE to be related to study treatment.

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 10.2.4.
- a subject develops a Grade 2 or greater allergic reaction in association with administration of rFIXFc 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 rFIXFc, with the exception of IV injection site thrombophlebitis

- a subject undergoes major surgery

Allergic reactions, including anaphylaxis, have been reported with FIX products. Hypersensitivity reactions have been reported with rFIXFc. These events often occur in close temporal relation with the development of FIX inhibitors. Subjects (as appropriate) and parents/legal guardians of subjects 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/legal guardians should be instructed to seek immediate medical care for the subject. The presence of inhibitors has been associated with allergic reactions with FIX replacement therapies, including with rFIXFc. Subjects experiencing allergic reactions should be evaluated for the presence of an inhibitor.

Subjects (as appropriate) and parents/legal guardians of subjects 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 14 (+7) days after the last dose of rFIXFc (up to last study visit/telephone call) must be reported to Quintiles Pharmacovigilance within 24 hours of the study site staff becoming aware of the event. Thereafter, the event should be reported to Quintiles Pharmacovigilance only if the Investigator considers it related to study treatment.

A report ***must be submitted*** to Quintiles Pharmacovigilance 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 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 as required, according to local law.

15.4. Procedures for Handling Special Situations

15.4.1. Pregnancy

The population under study is male; therefore, pregnancies will not be tracked.

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

15.4.2. Overdose

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

15.4.3. 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.

15.4.4. 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 SAE 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 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 of the study and the endpoints to be analyzed are listed 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 and Full Analysis Set (FAS), as appropriate. A subset of analyses may be performed based on the Supporting Analysis Set. Descriptions of the Safety Analysis Set and Supporting Analysis Set are provided in Section 16.5.1 and a description of the FAS is provided in Section 16.2.1. 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 rFIXFc study drug will be included in the FAS. Efficacy analyses will be based on the FAS including the data collected on or after the time of the first injection of rFIXFc study drug.

Subjects developing a confirmed positive inhibitor test after exposure to rFIXFc study drug (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 rFIXFc 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 rFIXFc 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 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, traumatic), location of the bleed, and spontaneous joint bleeding episodes, and for other subgroups of interest. The consumption of rFIXFc 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 their rFIXFc 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 rFIXFc, 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 exploratory endpoints (health outcomes).

16.3. Pharmacokinetics

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

PK parameters, such as IR, derived from assessments during ITI will be listed for each applicable subject. PK parameters (IR) for subjects undergoing ITI will be determined by analyses of the FIX 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 rFIXFc 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 rFIXFc, including study drug and/or commercially available rFIXFc. The primary safety analyses will be based on the Safety Analysis Set including the data collected on or after the time of the first injection of rFIXFc (study drug and/or commercially available rFIXFc).

The Supporting Analysis Set is defined as all subjects who receive at least 1 dose of rFIXFc study drug and meet the eligibility criteria (with screening FIX activity and inhibitor test results confirmed by the central laboratory). Selected safety analyses may be based on the Supporting Analysis Set including the data collected on or after the time of the first injection of rFIXFc study drug.

16.5.2. Methods of Analysis

16.5.2.1. Occurrence of Inhibitor Development

The analysis of inhibitor development will be based on the Safety Analysis Set, as defined in Section 16.5.1.

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 (CI). The main analysis will include all subjects who have received at least 1 dose of rFIXFc (study drug and/or commercially available rFIXFc). Further analyses will be presented for subjects who reach certain ED milestones, to be specified in the statistical analysis plan. For this latter analysis, both the numerator and denominator will include subjects who develop an inhibitor, even if they have not reached the specified ED milestone. One ED is defined as a 24-hour period in which a subject receives 1 or more doses of rFIXFc, with the time of the first injection of rFIXFc 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. Serious pretreatment events will be included and identified in the SAE listing, but only serious events occurring after the start of treatment will be summarized.

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 rFIXFc per subject will be summarized overall based on the Safety Analysis Set; selected analyses may be based on the Supporting Analysis Set.

16.6. Interim Analyses

There are no interim analyses planned for this study.

16.7. Sample Size Considerations

Hemophilia B is a rare disease. Because the size of the hemophilia population is limited, the sample size is based on clinical rather than statistical considerations. Taking into account the EMA CHMP Guideline [EMA (EMA/CHMP/BPWP/144552/2009) 2011] and in an effort to enroll a sufficient number of subjects to assess the efficacy and safety of rFIXFc in this population of primarily very young children, approximately 30 subjects will be enrolled to achieve at least 20 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, 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 Investigators to ensure that all aspects of institutional review are conducted in accordance with current applicable 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 or subject's legally authorized representative (e.g., parent or legal guardian), as applicable, in accordance with local practice and regulations. If a subject is receiving breast milk from his

mother, consent must also be obtained from the mother for collection of her concomitant medication data.

The background of the proposed study, the procedures, the benefits and risks of the study, and that study participation is voluntary for the subject must be explained to the subject (or the subject's legally authorized representative). The subject or his parents/legal guardians must be given sufficient time to consider whether to participate in the study.

Subjects or their 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.

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

A copy of the signed and dated ICF, and assent if applicable, must be given to the subject or the subject's legally authorized representative. The original signed and dated ICF will be retained with the study records. Local regulations must be complied with in respect to the final disposition of the original (wet signature) and copies of the signed and dated ICFs.

Confirmation of informed consent, and assent if applicable, 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 Investigators and Bioverativ to use and disclose protected health information (PHI, i.e., subject-identifiable health information) in compliance with local law.

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. Due to the rarity of hemophilia B, little is known about differences in the response to FIX products or the occurrence of inhibitors across racial and ethnic groups. However, such differences have been noted in patients with hemophilia A. In cross-sectional analyses of FVIII haplotypes, differences in the occurrence of inhibitors have been observed [Astermark 2005; Carpenter 2012]. Differential responses to FVIII products may occur in different haplotypes of FVIII that also differ across racial and ethnic groups [Viel 2009].

Study reports will be used for research purposes only. The subject will not be identified by name in the eCRF, study-related forms, study reports, or any related publications. 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 post study 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 or inspections. The Investigator will be expected to cooperate with any audit or inspection 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.

The 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 the Sponsor 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 electronic data capture tool within 5 business days.

In addition, subjects/parents/caregivers in the study will have EPDs to record information regarding each dose of rFIXFc administered to the subject for any reason at their home or locations other than the study site. The subject or 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 subjects or parents/caregivers enter dosing information immediately after an injection (Section 10.1.2).

19.1.4. Central Laboratories for Laboratory Assessments

Central laboratories have been selected by the Sponsor 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 subject consent form may require similar modifications (see Sections 17.2 and 17.3).

19.4. Ethics Committee Notification of Study Completion or Termination

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

19.5. Retention of Study Data

The minimum retention time for study records will meet the strictest standard applicable to that site, as dictated by any institutional requirements or local laws or regulations. Prior to proceeding with destruction of records, the Investigator must notify 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 off-site 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.

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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 IX Fc Fusion Protein (rFIXFc; BIIB029) in the Prevention and Treatment of Bleeding in Previously Untreated Patients With Severe Hemophilia B," 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)

N/A [redacted] 28AUG2018

Study Site (Print)

APPENDIX A. rFIXFc DOSING GUIDELINES FOR BLEEDING EPISODES

The Sponsor will review, analyze, and interpret FIX activity results from the central laboratory. Based on this review, the Sponsor will make a recommendation to the Investigator for the appropriate dose selection for the corresponding individual and treatment situation. The following table describes dosing guidance with rFIXFc for bleeding episodes.

DOSING GUIDELINES FOR rFIXFc THERAPY IN HEMOPHILIA B

Type of Hemorrhage	Factor IX Level Required (%)
Minor	
Epistaxis	25-30
Hemarthroses, uncomplicated	25-30
Superficial muscular	25-30
Superficial soft tissue	25-30
Moderate	
Epistaxis	35-50
Intramuscular with dissection	35-50
Soft tissue with dissection	35-50
Mucous membranes	35-50
Dental extractions	35-50
Hematuria	35-50
Hemarthroses, with limited motion	35-50
Major	
Epistaxis	60-100
Pharynx	60-100
Retropharynx	60-100
Retroperitoneum	60-100
Surgery	60-100
Central nervous system	60-100

APPENDIX B. ASSESSMENT OF RESPONSE TO BLEEDING

[redacted]

APPENDIX C. PHYSICIAN'S GLOBAL ASSESSMENT

[redacted]

APPENDIX D. PHYSICIAN ASSESSMENT OF RESPONSE TO TREATMENT DURING SURGERY

[redacted]