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PROTOCOL NUMBER: 9HB01EXT

PHASE OF DEVELOPMENT: 3

PROTOCOL TITLE: An Open-Label, Multicenter Evaluation of the Long-Term Safety and Efficacy of Recombinant Human Coagulation Factor IX Fusion Protein (rFIXFc) in the Prevention and Treatment of Bleeding Episodes in Previously Treated Subjects With Hemophilia B

EUDRA CT NO: 2011-003075-11

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Version 4

FINAL

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SIGNATURE PAGE

Protocol 9HB01EXT, Version 4, was approved by:

[redacted]

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Date

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1. SPONSOR INFORMATION AND CONTACT INFORMATION

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Local telephone and fax numbers for reporting to Quintiles Pharmacovigilance from each participating country will be provided separately to each site to be retained in the Investigator's Study File.

Please refer to the Study Reference Manual, Official Study Contact List for complete contact information.

2. LIST OF ABBREVIATIONS

AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AUC_{inf}	Area under the activity versus time curve from the time of treatment administration (zero) extrapolated to infinity
BU	Bethesda Units
BUN	Blood urea nitrogen
CHO-KLAT	Canadian Hemophilia Outcomes-Kids' Life Assessment Tool
Cl	Clearance
C_{max}	Maximum activity
CRO	Contract research organization
DHA	Directions for Handling and Administration
dL	Deciliter
eCRF	Electronic case report form
ED	Exposure day(s)
EDC	Electronic data capture
eDiary	Electronic patient diary (EPD)
EOT	End of Treatment
FIX	Factor IX
FIX:C	Factor IX coagulant activity
GCP	Good Clinical Practice
HIV	Human immunodeficiency virus
HJHS	Hemophilia Joint Health Score
ICF	Informed consent form
ICH	International Conference on Harmonisation
IU	International Units
IV	Intravenous
IXRS	Interactive Voice and Web Response System
Kg	Kilogram
MRT	Mean residence time
PHI	Protected health information
PK	Pharmacokinetics
PTP	Previously treated patient
QoL	Quality of life
rFIXFc	Recombinant human coagulation Factor IX fusion protein
SAE	Serious adverse event
SUSAR	Suspected unexpected serious adverse event
$t_{1/2}$	Half-life
US	United States
V_{ss}	Volume of distribution at steady-state
WBC	White blood count

WFH	World Federation of Hemophilia
WHO	World Health Organization

3. SYNOPSIS

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

Protocol Number:	9HB01EXT
Protocol Title:	An Open-Label, Multicenter Evaluation of the Long-Term Safety and Efficacy of Recombinant Human Coagulation Factor IX Fusion Protein (rFIXFc) in the Prevention and Treatment of Bleeding Episodes in Previously Treated Subjects With Hemophilia B.
Version Number:	4
Name of Study Treatment:	rFIXFc (BIIB029)
Study Indication:	Hemophilia B
Phase of Development:	3
Rationale for the Study:	To evaluate the long-term safety and efficacy of rFIXFc for the prevention and treatment of bleeding episodes in previously treated subjects with hemophilia B, and to allow subjects from the Phase 3 pivotal study (998HB102), the pediatric study (9HB02PED), or any other rFIXFc study (parent studies) to continue treatment with rFIXFc.
Study Objectives and Endpoints:	**Objectives** Primary: The primary objective of the study is to evaluate the long-term safety of rFIXFc in subjects with hemophilia B. Secondary: The secondary objective of this study is to evaluate the efficacy of rFIXFc in the prevention and treatment of bleeding episodes in subjects with hemophilia B. **Endpoints** Primary: The occurrence of inhibitor development. Secondary: • The annualized number of bleeding episodes per subject • The annualized number of spontaneous joint bleeding episodes per subject • The total number of days of exposure per subject per

year

- The consumption of rFIXFc as total dose per kg per subject per year
- Physician's global assessment of the subject's response to his treatment regimen using a 4-point scale
- Subject's/caregiver's assessment of response to the treatment of bleeding episodes using a 4-point scale

Endpoints for Major Surgeries:

- Investigator/Surgeon assessment of hemostatic response to surgery using the 4-point bleeding response scale
- Number of injections and dose per injection to maintain hemostasis during the surgical period
- Estimated blood loss (mL) during surgery and the post-operative period
- Number of blood product units transfused during surgery

Patient-Reported and Health Outcome Endpoints:

Subjects will be assessed only for those health outcomes and Quality of Life (QoL) parameters that they had been previously evaluated for in the parent study, and only for as long as they remain within the age range for the respective instrument. This could include the following:

- Haem-A-QoL
- Haemo-QoL
- Hemo-Sat-Patient Satisfaction Scale Version 15 (for parents/guardians of subjects less than 18 years of age
- Canadian Hemophilia Outcomes-Kids' Life Assessment Tool (CHO-KLAT)
    - Children, Version 2.0 (for children previously enrolled in study 9HB02PED who are less than 18 years of age).
    - Proxy, Version 2.0p (for parents/guardians of children who were previously enrolled in study 9HB02PED and are less than 18 years of age)
- EQ-5D-Y

- EQ-5D-3L

Other patient-reported and health outcomes related to hemophilia, as described in Section 6.2.4.

- Number of hospitalizations, excluding planned hospitalizations, elective surgery documented at Visit 1, and emergent surgery
- Number of emergency room visits
- Number of physician visits, excluding study visits
- Number of hospitalization days
- Number of days off work, school/daycare, or preschool
- Number of days off work for the parent/guardian or caregiver

Study Design:	This is an open-label, multicenter, long-term study of intravenous (IV) administration of rFIXFc in previously treated patients with hemophilia B, who completed the Phase 3 pivotal study (998HB102), pediatric study (9HB02PED), or any other trial with rFIXFc. Treatment will be administered as a prophylactic (weekly, individualized, or personalized) regimen or on-demand (episodic) treatment.
Rationale for Dose and Schedule Selection:	The choice of treatment schedule will be based on the clinical profile of the subject and by the trough or peak (recovery) FIX activity values observed in the parent study, if needed. Subjects 12 years of age or older are permitted to change their regimen from prophylaxis to on-demand and from on-demand to prophylaxis during the study. Subjects less than 12 years of age will receive a prophylactic regimen and will not have the option to change to on-demand treatment until they reach the age of 12 years. All treatment regimen changes will be discussed with the subject (or parent/guardian, as applicable). All treatment regimen changes require the approval of the Sponsor Medical Monitor. The starting dose in study 9HB01EXT may be based on a subject's dose and dosing interval from the parent rFIXFc study. In the completed Phase 3 pivotal study (998HB102), doses between 20 IU/kg and 100 IU/kg were generally well tolerated. In the pediatric study (9HB02PED), a starting dose of approximately 50 IU/kg to 60 IU/kg is being administered, with dose adjustments based upon trough and recovery levels obtained at scheduled visits. The dose for routine prophylaxis and treatment of bleeding episodes may be adjusted up to 100 IU/kg and the interval decreased to twice a week. In addition, higher doses of up to 150 IU/kg may be used to maintain adequate FIX activity and to prevent bleeding (e.g., during surgery).

Treatment Regimens:

For the purpose of analysis, the treatment regimen in 9HB01EXT means the actual treatment regimen(s) that subjects follow over the course of the study (i.e., not the regimen they started on in the parent study).

On-demand (Episodic) Treatment

The individual dose of rFIXFc to treat bleeding episodes will be based on the subject's clinical condition, type and severity of the bleeding event, and in some cases, FIX peak (recovery) levels. Pharmacokinetic (PK) data and dosing levels from the parent studies can also be used to guide dosing decisions. Subjects less than 12 years of age will receive a prophylactic regimen and will not have the option to receive on-demand treatment until they reach the age of 12 years during the study.

Prophylaxis Regimens

The Investigator may consider the following options for prophylaxis to target a FIX trough of up to 5% above baseline, but is encouraged to use the lowest effective dose targeting a FIX trough level between 1% and 3%. If bleeding episodes occur at FIX trough levels of 1% to 3%, further adjustments to dose or interval over the course of the study will target trough levels of up to 5%.

- Option 1: Weekly Prophylaxis

Dosing is approximately 20 IU/kg to 100 IU/kg every 7 days. The dose should be based on the subject's clinical profile observed in the parent rFIXFc study and his individual PK profile, trough, and/or peak (recovery) values.

- Option 2: Individualized Prophylaxis

Dosing is approximately 100 IU/kg every 8 to 16 days, or 2 times per month. The dosing interval should be based on the subject's clinical profile observed in the parent rFIXFc study, and his individual PK, trough, and/or peak (recovery) values.

- Option 3: Personalized Prophylaxis

If optimal prophylaxis dosing cannot be achieved using either of the above options, the Investigator may further personalize dosing to meet the needs of individual subjects.

The Investigator may consider the following personalized dosing options:

- Addition of "prevention" doses prior to strenuous activity.

- Targeting a FIX trough level of >5%, if warranted by the bleeding history and/or activity level.

- Dosing 2 times per week, e.g., approximately 25 IU/kg twice weekly vs. approximately 50 IU/kg once weekly, for subjects who may have better control with such a regimen. For pediatric subjects <12 years of age, the dose may be adjusted up to 100 IU/kg twice weekly.

The Investigator is not limited to the options above, and should consult the Medical Monitor for further consideration of a subject's dosing options. The personalized prophylaxis dosing option will require consultation with the Medical Monitor.

Details for each dosing option, including, if applicable, date of change, new dose and/or dosing interval, and reason(s) for the regimen change will be recorded on the appropriate electronic case report form (eCRF) each time a change is made by the Investigator.

Surgery/Rehabilitation

If a subject requires surgery during this study, either emergent or elective, he may be treated with the dose and regimen of rFIXFc deemed appropriate for the type of surgery.

All major surgeries must take place in a center that can provide study treatment, trained study personnel, post-operative assessments and hematological consultation by the Investigator or Sub-investigator. If surgery does not take place in such a setting, the subject will be withdrawn from the study. Specific provisions apply when a subject requires major surgery.

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

- Major surgery is defined as any surgical procedure (elective or emergent) that usually, but not always, involves general anesthesia and/or respiratory assistance, in which a major body cavity is penetrated and exposed, or a substantial impairment of physical or physiological functions is produced (e.g., laparotomy, thoracotomy, craniotomy, joint replacement, or limb amputation).

- Minor surgery is defined as any surgical procedure (elective or emergent) that does not involve general anesthesia and/or respiratory assistance (e.g., minor dental extractions, incision, and drainage of abscess, joint or other injections, or simple excisions).

All major surgeries will be reported as serious adverse events (SAEs).

Rehabilitation period

	If surgery-related dosing is to be continued during post-operative rehabilitation, the dose of rFIXFc will be adjusted to achieve a trough at a sufficient level to maintain hemostasis, including during physical therapy. These doses will be captured in the subject's electronic patient diary (eDiary). Subjects will return to a regular rFIXFc regimen once all dosing for the post-operative period has been completed. For subjects undergoing major surgery, a visit is required 1-2 weeks after surgery (Visit 3). Visit 4 (Last Post-Operative Visit) occurs when the subject returns to a regular rFIXFc regimen as determined by the Investigator, and is required only if the subject did not return to a regular rFIXFc regimen at Visit 3. For minor surgery, Visits 3 and 4 are not performed.
Study Location:	Global
Number of Planned Subjects:	Approximately 120 subjects are planned to be treated in the study.
Study Population:	This study will be conducted in previously treated adult and pediatric subjects with hemophilia B who have participated in a previous rFIXFc clinical study. Detailed criteria are described in the body of the protocol.
Duration of Treatment and Follow-up:	Subjects are expected to be followed through at least 100 exposure days (EDs) to rFIXFc and may further continue in this study for up to 4 years or until rFIXFc is commercially available in the applicable participating country.
Definition of Dose-Limiting Toxicity:	No dose-limiting toxicity for rFIXFc has been identified.
Statistical Methods:	In general, subjects who enroll from the parent studies will have their study data integrated with their data for 9HB01EXT. A parent study is defined as a study where subjects may be enrolled into 9HB01EXT after study completion or at a time specified in the protocol. **Demography and Baseline Disease Characteristics** The analysis of demography and baseline disease characteristics will be based on the Safety Analysis Set. The Safety Analysis Set includes all subjects who have received at least one dose of rFIXFc. Demographics and baseline disease characteristics will be summarized categorically and/or with descriptive statistics, as appropriate, using the data at the entry of the parent studies. **Efficacy** Subjects who receive at least one dose of rFIXFc will be included in the Full Analysis Set (FAS). Efficacy analyses will be based on the FAS. Bleeding episodes will be annualized for each subject, and then summarized and tabulated by treatment arm, treatment regimen, or

age cohort, as appropriate, for the parent study and the 9HB01EXT treatment regimen(s). These analyses will be performed for each type of bleed. The number of spontaneous joint bleeding episodes and the consumption of rFIXFc will be annualized in a similar fashion and tabulated.

Analysis of surgery endpoints will be performed for subjects who had surgery during the study, either emergently or electively. Summary statistics of surgery endpoints will be provided for the surgical/rehabilitation period.

The periods in which data will be used for efficacy and surgical rehabilitation analyses will be defined in the statistical analysis plan. Data on bleeding and rFIXFc consumption will be based on the efficacy period; surgical evaluations will be based on the surgical/rehabilitation period.

Patient-Reported and Health Outcomes

Endpoints for patient-reported outcomes (Haem-A-QoL, Haemo-QoL, Hemo-Sat-Patient, CHO-KLAT Children, CHO-KLAT Proxy, EQ-5D-Y and EQ-5D-3L) will be analyzed in a separate report. These endpoints will be analyzed by summarizing actual values and changes from baseline, as appropriate.

Summary statistics of health outcome endpoints will be tabulated at each collection timepoint.

Safety

The Safety Analysis Set will include all subjects with at least one dose of rFIXFc. For the analysis of safety, data in 9HB01EXT will be integrated with data from the parent studies, unless specified otherwise. The incidence of adverse events (AEs) will be tabulated overall, by severity, and by relationship to treatment. In addition, the incidence of AEs will be presented by ED intervals. Findings in clinical lab values will be summarized by descriptive statistics.

The proportion of subjects with inhibitors during rFIXFc administration will be provided with the exact (Clopper-Pearson) 2-sided, 95% confidence interval.

Interim Analysis: Interim analyses will be conducted during the study, as needed. Analyses will be descriptive in nature. No formal comparisons are planned and no hypotheses will be formally tested. The study has an open label design and thus, personnel conducting interim analyses will not be blinded to treatment assignments.

Sample Size Determination: This is an extension study. The samples size is based on sample sizes of studies 998HB102, and 9HB02PED and is estimated to be approximately 120 subjects, but may be increased based upon subject participation in other rFIXFc studies.

Study Stopping Rules: The Sponsor may terminate this study at any time, after informing Investigators.

Study stopping is required if any of the following occur:

- Three subjects develop a high-titer inhibitor (i.e. ≥5.00 BU/mL), identified and confirmed on 2 separate samples drawn approximately 2 to 4 weeks apart, and performed by the central laboratory using the Nijmegen-modified Bethesda assay. This number can be adjusted based on sample size when more subjects might be included into this trial from other rFIXFc studies.

- An unexpected, serious, or unacceptable risk to study subjects.

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 Sponsor's Safety Surveillance Team, it is determined that the study should be permanently discontinued, then subjects will attend a final visit.

4. SCHEDULE OF EVENTS FOR STUDY 9HB01EXT

4.1. Screening and Treatment Period

Table 1: Screening and Treatment Period

Tests and Assessments[1]	Visit 1[2]	Visit 2 Month 6 (±2 weeks)	Visit 3 Month 12 (±2 weeks)	Visit 4 Month 18 (±2 weeks)	Visit 5 Month 24 (±2 weeks)	Visit 6 Month 30 (±2 weeks)	Visit 7 Month 36 (±2 weeks)	Visits Semi-Annually (Every 6 months) (±2 weeks)
Informed Consent and Assent Forms	X							
Eligibility Verification	X							
Medical and Surgical History and Demographics[3]	X							
Physical Examination[4]	X		X		X		X	X
Vital Signs[5]	X	X	X	X	X	X	X	X
Height	X		X		X		X	X
Weight	X	X	X	X	X	X	X	X
rFIXFc dosing/dispensation/accountability[6]	X	X	X	X	X	X	X	X
Nijmegen-modified Bethesda assay (inhibitor assay)[7]	X	X	X	X	X	X	X	X
Anti-rFIXFc antibody[7]	X	X	X	X	X	X	X	X
Hematology[7,8]	X	X	X	X	X	X	X	X
Blood Chemistry[7,9]	X	X	X	X	X	X	X	X
FIX activity[7,10]	X	X	X	X	X	X	X	X
DNA-Based Testing[11]	X							
QoL Questionnaires[12]	X	X	X	X	X	X	X	X
Health Outcomes[13]	X	X	X	X	X	X	X	X
Subject eDiary Review[13]	X	X	X	X	X	X	X	X
Physician's Assessment of Response	<<<<<<<<<<<<<<<<<<<<<<<< Ongoing >>>>>>>>>>>>>>>>>>>>							

Tests and Assessments[1]	Visit 1[2]	Visit 2 Month 6 (±2 weeks)	Visit 3 Month 12 (±2 weeks)	Visit 4 Month 18 (±2 weeks)	Visit 5 Month 24 (±2 weeks)	Visit 6 Month 30 (±2 weeks)	Visit 7 Month 36 (±2 weeks)	Visits Semi-Annually (Every 6 months) (±2 weeks)
to Individual Bleeding Episodes Treated in Clinic								
Physician's Global Assessment of Response to the Treatment Regimen	X	X	X	X	X	X	X	X
HJHS[14]	X		X		X		X	X
AE/SAE Monitoring and Recording	X	Monitor and record at all visits; telephone call every 2 months for AE/SAE assessments						
Concomitant Therapy/Procedures Recording	X	Monitor and record at all visits; telephone call every 2 months						

AE=adverse events; HJHS=Hemophilia Joint Health Score; QoL=quality of life; SAE-serious adverse events

Table footnotes are presented on page 24.

Table 1: Screening and Treatment Period, continued:

Tests and Assessments[1]	Unscheduled Visit[15]	Final Study Visit/Early Termination Visit	Follow-Up[16] 14 (+7) days after last dose of study drug
Physical Examination[4]		X	
Vital Signs[5]	X	X	
Height		X	
Weight		X	
rFIXFc dosing/dispensation/accountability[6]	X	X	
Nijmegen-modified Bethesda assay (inhibitor assay)[7]		X	
Anti-rFIXFc antibody[7]		X	
Hematology[7,8]		X	
Blood Chemistry[7,9]		X	
FIX activity[7,10]		X	
QoL Questionnaires[12]		X	
Health Outcomes[13]		X	
Subject eDiary Review[13]	X	X	
Physician's Assessment of Response to Individual Bleeding Episodes Treated in Clinic	<<<<<<<< ongoing >>>>>>>>		
Physician's Global Assessment of Response to the Treatment Regimen	X	X	
HJHS[14]		X	
AE/SAE Monitoring and Recording	Monitor and record at all visits; telephone call every 2 months for AE/SAE assessments		X
Concomitant Therapy/Procedures Recording	Monitor and record at all visits; telephone call every 2 months		X

AE=adverse events; HJHS=Hemophilia Joint Health Score; QoL=quality of life; SAE-serious adverse events

Table footnotes are presented on page 24.

Footnotes for Screening and Treatment Period

1. Subjects who enroll into 9HB01EXT will be assessed only for those parameters at had been previously assessed in the parent study.
2. The End of Treatment (EOT) visit for the parent study may serve as the Screening Visit for the extension study. Written informed consent and subject assent, if applicable, for participation in the extension study must be obtained at this visit before any extension study-related procedures are conducted. The subject or his Parents/legal guardians should receive the informed consent information prior to this visit to allow adequate time for review at home, and discussion with the Investigator. Data on medical history, demographics, screening tests, ongoing adverse events and concomitant therapy, and EOT tests and assessments will be transferred from the parent rFIXFc study, so it will not be necessary to repeat these assessments at Visit 1. An HJHS or modified HJHS assessment, as appropriate, should be performed at Visit 1 in ALL subjects. Study eligibility must be verified prior to study enrollment. Subjects who enroll with a gap of greater than 37 days following the EOT Visit for the previous study should have all laboratory assessments performed and reviewed by the Investigator at Visit 1, prior to dosing with rFIXFc, to assess safety and inclusion/exclusion parameters. The time allotted for Visit 1 may span a sufficient interval to allow for laboratory results to be reviewed and confirmed as suitable by the Investigator. Otherwise, more than 1 clinic visit may be required prior to dosing with rFIXFc.
3. Medical and surgical history includes any significant medical condition and/or any significant surgical histories that occurred prior to the subject enrollment in the parent study.
4. Physical examination will include assessments of the skin, head, eyes, ears, nose, throat (HEENT), lymph, neck, chest/lungs, heart, vascular system, abdomen, musculoskeletal and neurological function, extremities, and joints. Following Visit 7, physical examination will be performed on an annual basis.
5. Vital signs assessments include blood pressure, pulse rate, respiratory rate and temperature (°C), and should be taken after the subject has been resting supine for 5 minutes. At dosing visits, vital signs should be measured pre-injection and post-injection.
6. Subjects will receive supplies of rFIXFc for home administration from the study site at and between visits; each time, the study site staff will perform full medication exchange and accountability with the subject or the subject's caregiver. See Section 16 for information on planning and the dispensation process, and on supply accountability.
7. To be performed at the central laboratory. For FIX inhibitor and anti-rFIXFc antibody testing, a washout of at least 72 hours is recommended. For subjects who have fewer than 50 exposure days (EDs) with rFIXFc following completion of Visit 1, a visit may be conducted to perform inhibitor testing at the time subjects reach 10 to 15 EDs, 50 to 75 EDs, and after 100 EDs, as applicable (The total exposure day count[ED] is the number of rFIXFc exposure days from the previous rFIXFc study and this extension study, combined). If the timing for inhibitor testing does not coincide with a scheduled visit, an unscheduled visit may be conducted. Blood samples will be collected at each visit for back-up and archiving for future testing (if required) of immunology or further coagulation assays, or for clarification of any clinical or laboratory AE. Additional inhibitor and anti-rFIXFc antibody testing should also be performed when deemed clinically relevant.
8. Hematology includes: white blood cells (WBC), differential, platelet count, hemoglobin, and hematocrit.
9. Blood chemistry includes: Electrolytes (sodium, potassium, chloride), glucose, total protein, total bilirubin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), blood urea nitrogen (BUN), and serum creatinine.
10. For weekly, individualized, and personalized prophylaxis regimens: FIX activity is to be measured at the trough immediately prior to the infusion and at peak (recovery) 30 (±5) minutes from the start of injection. For on-demand treatment: FIX activity should be measured at the discretion of the Investigator.
11. The collection of a sample for DNA-based testing is optional and may occur at any time during the study, not exclusively at Visit 1.
12. Patient-reported outcomes should be completed only if they were conducted during the parent study. Questionnaires should be completed every 6 months, at scheduled clinic visits. Questionnaires will be provided under a separate cover.
13. Changes in patient-reported health outcomes assessed during the parent study are to be queried in the subject's electronic patient diary (eDiary) on an ongoing basis, and details are to be recorded in the electronic case report form (eCRF).

14. Subjects entering the extension study from 998HB102 should continue to use the Modified Hemophilia Joint Health Score. Subjects entering the extension study from 9HB02PED should continue to use the HJHS Version 2.1. Subjects entering the extension study from other parent studies should continue to use the Joint Health Score instrument that is consistent with his parent study. Following Visit 7, the HJHS assessment will continue to be performed annually. The HJHS assessment is not required at the Final Study Visit if it was performed within the last 9 months.
15. Unscheduled visits may be necessary during the study, as determined by the Investigator, for reasons that may include repeating safety assessments, repeating blood sampling, testing FIX activity levels if required, or changing dose/regimen. For subjects from a parent study who undergo surgery and enter the extension study before completing their Last Post-Operative Visit, an unscheduled visit may be conducted to perform the Last Post-Operative Visit assessments when the subjects switch from their post-surgery dosing regimen to a regimen outlined in Section 5.3.2 (see Section 5.3.3 for list of assessments). Inhibitor testing will be performed at the time subjects reach 10 to 15 EDs, 50 to 75 EDs, and after 100 EDs, as applicable (The total ED is the combined rFIXFc exposure days from a previous rFIXFc study and this extension study). If the timing for inhibitor testing does not coincide with a scheduled visit, an unscheduled visit may be conducted.
16. A follow-up telephone visit is required 14 (+7) days after the last dose of study rFIXFc to monitor AEs, SAEs, and concomitant medications and therapies. This 14 (+7) day follow-up visit is not required if a subject ends his participation in the extension study to enroll into another rFIXFc study, however, a final visit/early termination visit is required.

4.2. Surgery Visits

Table 2: Surgery Visits

Tests and Assessments[1]	Pre-Surgery[2] Visit 1 Week -12 to Week -1 prior to Surgery	Visit 2 Day of Surgery	Visit 3 1-2 Weeks Post Surgery[3]	Visit 4 Last Post-Operative Visit[4]
Physical Examination[5]	X	X		X
Weight	X	X	X	X
Vital Signs[6]	X	X	X	X
Hematology[7]	X	X	X	X
Blood Chemistry[7]	X	X	X	X
Subject's Assessment of Response[8]	<<<<<<<< ongoing as applicable >>>>>>			
Investigator/Surgeon Assessment of Hemostatic Response[9]		X		
FIX activity[10]	X	X	X	X
Nijmegen-modified Bethesda assay (inhibitor testing)[4]	X	X	X	X
Anti-rFIX Antibody Assay[4]	X	X	X	X
rFIXFc Administration	X	X	X	X
AE/SAE Monitoring and Recording	X	X	X	X
Concomitant Medications/ Procedures Recording	X	X	X	X

AE=adverse events; SAE-serious adverse events

Footnotes for Surgery Visits

1. All tests and assessments should be collected for major surgery and for minor surgery when available. Subjects may be allowed to have a PK evaluation performed by the central or local laboratory prior to surgery if needed, in the opinion of the Investigator.
2. To be assessed prior to surgery.
3. Visit 3 (1-2 Weeks Post Surgery) and Visit 4 (Last Post-Operative Visit) are not performed for subjects who undergo minor surgery. For major surgery, Visit 4 occurs when the subject returns to a regular rFIXFc regimen as determined by the Investigator, and is not required if the return to a regular rFIXFc regimen occurs at Visit 3.
4. For surgery, inhibitor and anti-rFIXFc antibody testing is to be performed 2 to 4 weeks prior to surgery, pre-operatively on the day of surgery, 1-2 weeks after surgery, and at the last post-operative visit. For FIX inhibitor and antibody testing, a washout of at least 72 hours is recommended. For minor surgery, the testing is performed at investigator's discretion.
5. Physical examination will include assessments of the skin, head, eyes, ears, nose, throat (HEENT), lymph, neck, chest/lungs, heart, vascular system, abdomen, musculoskeletal and neurological function, extremities, and joints. Following Visit 7, physical examination will be performed on an annual basis.
6. Vital signs assessments include blood pressure, pulse, respiratory rate and temperature (°C), and should be taken after the subject has been resting supine for 5 minutes. At dosing visits, vital signs should be measured pre-injection and post-injection.
7. To be performed at the central laboratory. Hematology includes: WBC, differential, platelet count, hemoglobin, and hematocrit. Blood chemistry includes: Electrolytes (sodium, potassium, and chloride), glucose, total protein, total bilirubin, ALT, AST, ALP, BUN, and serum creatinine.

8. Subjects who require post-operative rFIXFc treatment for a bleeding episode at home will record their assessment of the response to treatment in the eDiary; this assessment is to be made approximately 8 to 12 hours from the time the rFIXFc injection was given to treat the bleeding episode and prior to any additional doses of rFIXFc given for the same bleeding episode.
9. The Investigator/Surgeon will record the assessment of the subject's response to treatment during surgery using a 4-point scale. This assessment will be done 24 hours after surgery. See Appendix C and Appendix E.
10. FIX activity levels should be measured prior to administration of the pre-operative (loading) dose of rFIXFc, and at 30 ±5 minutes post-dosing. A repeat sample may be taken approximately 6 to 9 hours after the loading dose or at an interval based on the local standard of care for subsequent rFIXFc dosing. During the subject's hospitalization, FIX activity will be measured daily at the local laboratory, and a plasma aliquot will be prepared for each blood sample for subsequent analysis at the central laboratory.

5. INTRODUCTION

9HB01EXT is an extension study designed to assess the long-term safety and efficacy of rFIXFc in previously treated subjects with hemophilia B. Male subjects of all ages who have completed any parent study with rFIXFc (998HB102, 9HB02PED, and any other rFIXFc study) may be eligible for enrollment in this study.

The 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, or Christmas disease, is caused by a deficiency of functional clotting Factor IX (FIX). This recessively inherited coagulation disorder is due to an X-chromosome mutation carried by females and expressed mainly in males, which affects approximately 1 in 50,000 births worldwide [Skinner 2012]. A deficiency of FIX results in subjects' bleeding into joints, soft tissue, and muscle that can be associated with trauma or can occur in the absence of trauma (spontaneous bleeding). Depending on the severity of the bleeding, it can also pose a life-threatening situation (e.g. intracranial hemorrhage, other internal bleeding) for a subject if not treated appropriately. FIX, a serine protease, and factor VIII, a cofactor for FIX, work in concert to activate Factor X; this activation is a central step in the clotting cascade.

5.1.1. Therapies for Hemophilia B

There is no available cure for hemophilia B, so treatment focuses on the replacement of FIX with FIX-containing coagulation products, administered intravenously (IV), to promote clotting. The goal of treatment with FIX-containing coagulation products is to raise the circulating level of FIX to the lowest effective dose to achieve either resolution of bleeding (on-demand [episodic] treatment) or prevention of bleeding (prophylaxis treatment) [Roberts 1993; WFH 2005; MASAC March 2009]. The frequency of administration of FIX products differs among subjects and is usually tailored to the subject's clinical status, taking into consideration the type of bleeding episode, frequency of bleeding, and goal of treatment for the subject. The dose of FIX required also varies and is based on ongoing clinical experience and guidelines established by organizations such as the National Hemophilia Foundation of the United States and the WFH [Roberts 1993; Srivastava 2013] .

The use of FIX-containing, plasma-derived coagulation products, available for almost 40 years, has led to vast improvements in the care of hemophilia B, subject life expectancy, and quality of life for people with hemophilia. Risks of plasma-derived products include subject infection with serious blood-borne pathogens, including human immunodeficiency virus (HIV) and hepatitis B and C, as well as thrombosis. Recombinant coagulation products with no animal- or human-plasma-derived proteins, developed more recently, have the safety advantage that the risk of disease transmission is minimal [Roth 2001; White 1998].

Identified priorities for hemophilia B therapy include the development of more convenient dosing options [Lambert 2007] and investigation into modified FIX agents with a longer half-life to decrease injection frequency. Current therapy is focused on home therapies, which, taken prophylactically or administered at the onset of a bleeding episode, reduce short-term disability and long-term joint damage and improve subjects' overall quality of life and functional independence [Colvin 2008].

5.1.2. rFIXFc

rFIXFc (BIIB029) is a recombinant coagulation Fc fusion protein, comprised of FIX covalently attached to the Fc domain of human IgG, that is in development as a long-acting version of rFIX for the treatment of hemophilia B. rFIXFc has been tested in 14 subjects with severe, previously treated hemophilia B in a Phase 1/2a study and 123 subjects aged 12 years and older in a completed Phase 3 study (998HB102). Another Phase 3 study is currently ongoing in pediatric subjects (9HB02PED). Preclinical and clinical experience, to date, has shown an extended half-life of FIX activity compared with commercially available recombinant FIX products. This extended half-life may reduce the frequency of IV injections required for prevention of bleeding and for treatment for bleeding episodes in hemophilia B subjects. A therapy with these characteristics may also improve treatment compliance and quality of life.

5.1.3. Summary of Clinical Experience with rFIXFc

Completed study SYN-FIXFc-07-001 was a Phase 1/2a, open-label, multicenter, safety, dose-escalation study evaluating the safety and PK of a single dose of rFIXFc in 14 adult male previously treated patients (PTPs) with severe hemophilia B (defined as ≤2 IU/dL [≤2%] endogenous FIX). In this study, rFIXFc was given in escalating doses at 6 dose levels, ranging from 12.5 to 100 IU/kg. In this dose range, a dose-linear PK profile and a prolonged rFIXFc of $t_{1/2}$ were demonstrated.

A single dose of rFIXFc, ranging from 1 to 100 IU/kg, was demonstrated to be safe and well tolerated in the study population. Adverse events were distributed evenly across treatment groups, and were mostly mild and not related to treatment. Two serious adverse events (SAEs) occurred, depression and abdominal adhesions; neither event was considered related to the study drug, and both were resolved with treatment. No deaths were reported during the study. Increased thrombin-antithrombin complex (TAT) levels in 2 subjects were not considered to be related to the study drug, but rather, to a minor ex vivo perturbation. None of the subjects tested positive for FIX inhibitors or anti-FIXFc antibodies at any time during the study.

In addition, a Phase 3 study in previously treated subjects aged 12 years or older with severe hemophilia B was recently completed (Study 998HB102). A total of 123 subjects in the Phase 3 study received rFIXFc as prophylaxis or on-demand treatment, and/or for perioperative management during the study. Of the 123 subjects evaluated in the Phase 3 study, 115 were treated for at least 26 weeks and 56 were treated for at least 52 weeks. There was a reduction in annualized bleeding rate (ABR) of 83% for subjects in the fixed weekly prophylaxis arm and a reduction of 87% for subjects in the individualized interval prophylaxis arm, compared to the on-demand treatment arm, and based on a negative binomial model.

Compared with BeneFIX®, rFIXFc demonstrated an improved PK profile. The geometric mean elimination $t_{½}$ of rFIXFc of 82.12 hours was 2.43-fold longer ($p<0.001$) than that of BeneFIX at 33.77 hours. Consistent with the prolonged $t_{½}$, the mean residence time (MRT) of rFIXFc was 2.39-fold longer ($p<0.001$) than BeneFIX, resulting in a 2.21-fold extension of Time to 1% trough ($p<0.001$) for rFIXFc, compared with BeneFIX.

rFIXFc was well tolerated in the Phase 3 study. No subject developed FIX inhibitors. Common AEs observed were consistent with those expected in patients with hemophilia B. Adverse drug reactions were mild and manageable, and the majority were not treatment limiting. Two subjects (1.6%) were reported to have discontinued from the study due to AEs: One subject required surgery for an infected knee prosthesis (device-related infection) and the other subject suffered injuries in a motorcycle accident (road traffic accident). Both were considered unrelated to rFIXFc treatment. There were no allergic reactions of Grade 2 or greater or serious vascular thrombotic events. One SAE, obstructive uropathy, was assessed by the Investigator as possibly related to treatment with rFIXFc. The event resolved with hydration and the subject completed the Phase 3 Study (998HB102).

Study 9HB02PED (referred to as the pediatric study) is an open-label, multicenter study evaluating the safety, PK, and efficacy of rFIXFc in previously treated pediatric patients with severe hemophilia B, who are <12 years of age, and have at least 50 EDs to FIX products prior to enrollment. Approximately 26 male subjects (13 subjects <6 years of age and 13 subjects 6 to <12 years of age) are planned to complete at least 50 weeks of prophylactic treatment to attain at least 50 EDs. At least 20 of these subjects (10 subjects <6 years of age and 10 subjects 6 to <12 years of age) will undergo an evaluation of the PK profile of pre-study FIX and rFIXFc. Subjects who complete this study will be offered enrollment into the extension trial described in this protocol.

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

5.2. Study Rationale

The results of the non-clinical data [Peters 2010], the Phase 1/2a study, and the Phase 3 study (998HB102) support further investigation of long-term repeat administration of rFIXFc in the prevention and treatment of bleeding episodes in hemophilia B subjects. This extension study will evaluate the long-term safety and efficacy of rFIXFc in subjects with hemophilia B and will allow subjects from the Phase 3 (998HB102) pivotal study, from the pediatric study (9HB02PED), and from other rFIXFc studies to continue treatment with rFIXFc.

5.3. Rationale for Dose and Schedule Selection

Subjects 12 years of age or older will follow a weekly, individualized, or personalized prophylaxis regimen or will be treated on-demand, based on the clinical profile of the subject and by the trough and/or peak (recovery) values, if needed. Subjects 12 years of age or older are allowed to change treatment regimens (for example, from prophylaxis to on-demand, or from on-demand to prophylaxis) during the course of the study. Subjects less than 12 years of age will

receive a prophylactic regimen and will not have the option to change to on-demand treatment until he reaches the age of 12 years. All treatment regimen changes will be discussed with the subject (and parent/guardian, as applicable). All treatment regimen changes require the approval of the Sponsor Medical Monitor. Details (including date of change, new dose and/or dosing interval, and reasons for the change) will be recorded on electronic case report forms (eCRFs).

The starting dose in 9HB01EXT may be based on the subject's results from his parent rFIXFc study. In the completed Phase 3 study, 998HB102, doses between 20 IU/kg and 100 IU/kg were administered. In the pediatric study (9HB02PED), a starting dose of approximately 50 IU/kg to 60IU/kg is being administered, with dose and interval adjustments up to 100 IU/kg twice a week, if necessary to maintain adequate FIX activity trough levels and prevent spontaneous bleeding events.

5.3.1. On-demand (Episodic) Treatment

The individual dose of rFIXFc to treat bleeding episodes will be based on the subject's clinical condition, type and severity of the bleeding event, and if indicated, FIX levels. A subject's pharmacokinetic (PK) profile and dosing levels from the parent study may also be used to guide dosing decisions. Subjects <12 years of age, entering from another rFIXFc study, will not be offered this option, but can opt to receive on-demand treatment when they reach the age of 12 years during the study.

Please refer to Appendix A for guidance on dosing decisions.

5.3.2. Prophylaxis Regimens

The Investigator may consider the following options for prophylaxis to target a FIX trough of up to 5%, but is encouraged to use the lowest effective dose targeting a FIX trough level between 1% and 3%. If bleeding episodes occur at FIX trough levels of 1% to 3%, further adjustments to dose or interval over the course of the study will target trough levels of up to 5%. In pediatric subjects <12 years of age, doses may be adjusted up to a maximum prophylactic dose of 100 IU/kg, with the interval decreased to twice a week, if necessary to maintain adequate FIX activity trough levels and prevent spontaneous bleeding events. Details for each dosing option, including, if applicable, the date of change, new dose and/or dosing interval, and reason(s) for the regimen change, will be recorded on the appropriate eCRF each time a change is made.

Option 1: Weekly Prophylaxis

Dosing is approximately 20 IU/kg to 100 IU/kg every 7 days. The dose should be based on the subject's clinical profile observed in the parent rFIXFc study and his individual pharmacokinetic profile (PK), trough, and/or peak (recovery) values.

- Option 2: Individualized Prophylaxis

Dosing is approximately 100 IU/kg every 8 to 16 days, or 2 times per month. The dosing interval should be based on the subject's clinical profile observed in the parent rFIXFc study, and his individual PK, trough, and/or peak (recovery) values.

- Option 3: Personalized Prophylaxis

If optimal prophylaxis dosing cannot be achieved using either of the above options, the Investigator may further personalize dosing to meet the needs of individual subjects.

The Investigator may consider the following personalized dosing options:

- Addition of "prevention" doses prior to strenuous activity.
- Targeting a FIX trough level of >5%, if warranted by the bleeding history and/or activity level.
- Dosing 2 times per week, e.g. 25 IU/kg, twice weekly, vs. 50 IU/kg, once weekly, for subjects who may have better control with such a regimen. For pediatric subjects <12 years of age, the dose may be adjusted up to 100 IU/kg twice weekly.

The Investigator is not limited to the options above, and should consult the Medical Monitor for further consideration of a subject's dosing options. The personalized prophylaxis dosing option will require consultation with the Medical Monitor.

Details for each dosing option, including, if applicable, date of change, new dose and/or dosing interval, and reason(s) for the regimen change will be recorded on the appropriate eCRF each time a change is made.

5.3.3. Surgery and Rehabilitation

If a subject requires emergent or elective surgery while participating in this study, he may be treated with the dose and regimen of rFIXFc deemed appropriate for the type of surgery. All major surgeries will be reported as SAEs.

All major surgical procedures must take place in a center that can provide study treatment, trained study personnel, post-operative assessments, and hematological consultation by the Investigator or Sub-Investigator. If the surgery does not occur in such a setting, the subject will be withdrawn from the study. See Section 10.1.3 for provisions for when a subject requires major surgery.

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

Subjects will return to a regular rFIXFc regimen once all dosing for the post-operative rehabilitation period has been completed. For subjects undergoing major surgery, a visit is required 1-2 weeks after surgery (Visit 3). Visit 4 (Last Post-Operative Visit) occurs when the

subject returns to a regular rFIXFc regimen, as determined by the Investigator, and is required only if the subject did not return to a regular rFIXFc regimen at Visit 3. For minor surgery, Visits 3 and 4 are not performed.

The surgical period will begin with the subject's first dose of rFIXFc given for the surgery (i.e., the pre-surgery dose). This is the pre-operative period of the surgery. The intra-operative period is defined as the time the surgery begins, to the time the surgery completes. The post-operative care period is defined as the time period following the completion of the surgery through the last dose of rFIXFc given for the surgery, as judged by the Investigator/Surgeon, including doses given to prevent bleeding during the post-operative rehabilitation period.

For subjects from a parent study who undergo major surgery and enter the extension study before completing their Last Post-Operative Visit from the prior rFIXFc study, an unscheduled visit may be conducted to perform the Last Post-Operative Visit assessments when the subjects switch from their post-surgery dosing regimen to a regular rFIXFc regimen (as outlined in Sections 5.3.1 and 5.3.2). The following assessments must be performed at that time:

- Physical examination
- Vital signs (blood pressure, pulse, respiratory rate and temperature [°C])
- Weight
- Hematology
- Subject's assessment of response
- FIX activity (to be measured at trough immediately prior to the injection and at peak [recovery] 30 [±5] minutes from the start of injection)
- Subject eDiary review
- Nijmegen-modified Bethesda assay (inhibitor assay)
- rFIXFc administration and accountability
- AE/SAE monitoring and recording
- Concomitant therapy/procedures recording

5.4. Potential Risks and Benefits

Please 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 long-term safety of rFIXFc in subjects with hemophilia B.

6.1.2. Secondary Objective

The secondary objective of this study is to evaluate the efficacy of rFIXFc in the prevention and treatment of bleeding episodes in subjects with hemophilia B.

6.2. Endpoints

6.2.1. Primary Endpoint

The primary endpoint is the occurrence of inhibitor development.

6.2.2. Secondary Endpoints

The secondary endpoints are as follows:

- The annualized number of bleeding episodes per subject
- The annualized number of spontaneous joint bleeding episodes per subject
- The total number of days of exposure per subject per year
- The consumption of rFIXFc as total dose per kg per subject per year
- Physician's global assessment of the subject's response to his treatment regimen using a 4-point scale
- Subject's/caregiver's assessment of response to the treatment of bleeding episodes using a 4-point scale

6.2.3. Major Surgery Endpoints

The major surgery endpoints are as follows:

- Investigator/Surgeon assessment of hemostatic response to surgery using the 4-point bleeding response scale

- Number of injections and dose per injection to maintain hemostasis during the surgical period
- Estimated blood loss (mL) during surgery and the post-operative period
- Number of blood product units transfused during surgery

6.2.4. Patient-Reported and Health Outcomes Endpoints

Subjects will be assessed only for those health outcomes and quality of life parameters that had been previously assessed in the parent study, and only for as long as they remain within the age range for the respective instrument. If a subject goes outside of the age range for a questionnaire, the subject should no longer complete it. The Investigator will administer the age-appropriate questionnaire at the appropriate visits. The patient-reported outcomes and health outcomes assessed may include the following:

Quality of Life (QoL) questionnaires:

- Haem-A-QoL [von Mackensen & Gringeri 2009]
- Haemo-QoL [von Mackensen 2004]
- Hemo-Sat-Patient Satisfaction Scale for parents/guardians, Version 15 [MAPI Research Institute 2009]
- Canadian Hemophilia Outcomes-Kids' Life Assessment Tool (CHO-KLAT)
    - Children, Version 2.0 (for children previously enrolled in study 9HB02PED who are less than 18 years of age).
    - Proxy, Version 2.0p (for parent/guardian of children who were previously enrolled in study 9HB02PED and who are less than 18 years of age)
- EQ-5D-Y [EQ-5D-Y 2011]
- EQ-5D-3L [EuroQol 1990]

Other patient-reported outcomes and health outcomes related to hemophilia

- Number of hospitalizations, excluding planned hospitalizations, elective surgery documented at Visit 1, and emergent surgery
- Number of emergency room visits
- Number of physician visits, excluding study visits
- Number of hospitalization days

- Number of days off work, school/daycare, or preschool
- Number of days off work for the parent/guardian or caregiver.

7. STUDY DESIGN

7.1. Study Overview

This is an open-label, multi-center, long-term study of intravenous (IV) administration of rFIXFc in previously treated patients (PTPs) with hemophilia B who have completed the Phase 3 pivotal study (998HB102), the pediatric study (9HB02PED), or any other study with rFIXFc. This is a global study and will be offered to all sites participating in these studies.

Based on estimated sample sizes from the parent studies, approximately 100 subjects from the completed Phase 3 study (998HB102) and approximately 20 subjects from the ongoing pediatric study (9HB02PED) may be eligible to enroll in this extension study. Additional subjects may transition from other rFIXFc studies into this extension study in the future. The End of Treatment (EOT) Visit from the previous study may serve as the screening visit for the extension study. Assessments performed at this visit will be used to confirm eligibility for participation in the extension study.

Study visits are scheduled at 6-month (±2 weeks) intervals following completion of Visit 1. Unscheduled visits may occur as deemed necessary by the Investigator. For subjects who enter the extension study and undergo surgery before completing their Last Post-Operative Visit from the parent rFIXFc study, the Last Post-Operative Visit assessments will be performed when the subjects switch from their post-surgery dosing regimen to a regimen outlined in Section 5.3.2 (see Section 5.3.3 for the list of assessments). Inhibitor testing will be performed at the time subjects reach 10 to 15 EDs, 50 to 75 EDs, and after 100 EDs, as applicable. The number of exposure days (EDs) for inhibitor testing is comprised of the number of exposure days from the parent study and this extension study, combined. If the timing for inhibitor testing does not coincide with a scheduled visit, an unscheduled visit may be conducted.

For subjects undergoing surgery, post-operative clinic visits may be more frequent. For subjects undergoing major surgery, a visit (Visit 3) is required 1-2 weeks after surgery (Visit 3 is not required for minor surgery). Visit 4 is required only if subjects who had major surgery did not return to a regular rFIXFc regimen at Visit 3. All major surgeries will be reported as SAEs. Scheduled visits will include safety and efficacy assessments and FIX activity measurements to assess trough and peak (recovery) (Section 4). In addition, the site will contact study subjects and/or caregivers by telephone on a bimonthly basis to review adverse events, treatment compliance, use of concomitant medications and therapies, and other issues.

Treatment will be self-administered as weekly, individualized, or personalized prophylaxis, or as on-demand treatment. Subjects 12 years of age or older will be able to switch from one regimen to another at scheduled or unscheduled visits during the study, per Investigator discretion. Subjects less than 12 years of age will receive a prophylactic regimen and will not have the option to change to on-demand treatment until they turn 12 years of age.

To ensure accuracy of FIX trough and/or peak (recovery) and inhibitor testing, subjects following a prophylaxis regimen should schedule clinic visits 72 hours after the previous dose of rFIXFc, whenever possible.

Subjects are expected to be followed through at least 100 exposure days (EDs) to rFIXFc and may further continue in this study for up to 4 years or until rFIXFc is commercially available in the applicable participating country.

7.1.1. Dose-Limiting Toxicity

No dose-limiting toxicities have been identified to date in humans receiving a single dose of rFIXFc up to 100 IU/kg. Also, no dose limiting toxicities were observed in preclinical animal studies where repeat doses of up to 1000 IU/kg were evaluated.

Doses higher than 100 IU/kg may be used in this study, for instance, in surgery, to achieve the required FIX levels to prevent bleeding. In pediatric subjects, the dose for routine prophylaxis and treatment of bleeding episodes may be adjusted up to 100 IU/kg at an interval no more frequent than twice weekly, although higher doses of up to 150 IU/kg may be used to achieve FIX activity to prevent bleeding. However, the maximum dose during surgery will not exceed the predicted accumulated C_{max} of approximately 150% of normal (normal ranges are 50-150% FIX activity).

An overdose of rFIXFc is defined as any single dose >150 IU/kg (see Section 15.4.1).

7.1.2. Inhibitor Testing

If inhibitor development is suspected at any time during the study (for example, because the expected plasma FIX activity levels are not attained, or bleeding is not controlled as expected following dosing), inhibitor testing will be performed by the central laboratory. The definition of a positive result for an inhibitor is any inhibitor (≥0.6 BU/mL) identified and confirmed on 2 separate samples, drawn approximately 2 to 4 weeks apart. Both tests must be performed by the central laboratory using the Nijmegen-modified Bethesda assay.

A high-titer inhibitor is defined as ≥5.00 BU/mL, identified and confirmed on 2 separate samples drawn approximately 2 to 4 weeks apart. Both tests must be performed by the central laboratory using the Nijmegen-modified Bethesda assay.

When an inhibitor test is performed at the local laboratory, an aliquot sample must be sent in parallel to the central laboratory.

For FIX inhibitor testing, a washout period of at least 72 hours is recommended.

Inhibitor testing will be performed at the time subjects reach 10 to 15 EDs, 50 to 75 EDs, and after 100 EDs, as applicable. The number of exposure days for inhibitor testing consists of the number of exposure days from the parent study and this extension study, combined. If the timing for inhibitor testing does not coincide with a scheduled visit, an unscheduled visit may be conducted.

7.1.3. Anti-rFIXFc Antibody Testing

Blood samples will be collected for back up and archiving for each subject at each inhibitor testing visit and may also be collected and archived at the time of any clinical event deemed relevant to rFIXFc antibody testing (see Table 1 and Table 2). In order to detect and characterize non-neutralizing antibodies that may react with rFIXFc, samples will be subject to an exploratory assay that differentiates between antibodies with specificities for rFIXFc, FIX (plasma FIX or BeneFIX®), and Fc. The electrochemiluminescent assay (ECLA) used for this test is approximately100-fold more sensitive than the Nijmegen-modified Bethesda assay.

7.1.4. Bleeding Episodes

If a subject experiences a bleeding event at any time during the study, he or his caregiver should follow the guidance for the treatment of bleeds, to be provided to each subject and/or caregiver. Guidance for study staff is provided in Appendix A. The type of bleed and the dose required to stop the episode will be recorded in the subject's electronic patient diary (eDiary, EPD).

In this study, when a subject reports a bleed or hemorrhage, and is treated with study drug, it will be classified as either spontaneous or traumatic by the subject or the subject's caregiver. The subject's eDiary will serve as the source document for bleeding episodes while on the study.

In this study, a bleed 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 treatment for the bleed, within which any symptoms of bleeding at the same location, or injections less than or equal to 72 hours apart, are considered the same bleed. Any injection to treat the bleed, taken more than 72 hours after the preceding one, will be considered the first injection to treat a new bleed at the same location. Any bleeding at a different location is considered a separate bleed, regardless of time from last injection.

Spontaneous bleeding episodes: Bleeding episodes should be classified as spontaneous if a subject records a bleeding event when there is no known contributing factor such as definite trauma or antecedent strenuous activity. The determination of "strenuous" is at the discretion of the Investigator. Target joints can have spontaneous bleeding episodes.

Traumatic bleeding episodes: Bleeding episodes should be classified as traumatic if a subject records a bleeding event when there is a known or believed reason for the bleed. For example, if a subject were to exercise strenuously and then have a bleed, even in the absence of any obvious injury, the bleed would be recorded as a traumatic bleed. Target joint bleeding episodes can be traumatic if a known action led to bleeding into the joint.

7.1.4.1. Information to be Recorded

The occurrence of bleeding in this study will be obtained from eDiaries and any medical records generated while the subject is receiving study treatment. The subject/subject's caregiver should enter eDiary information in a timely manner to facilitate appropriate medical review and dosing guidance. The clinical sites and study monitors will ensure that there is consistency between the subject's eDiary record and eCRFs. During clinical visits and bi-monthly telephone calls with

the subject/subject's caregiver, the Investigator will verify whether or not a bleed has occurred, and if any bleed was "spontaneous" or "traumatic." If, following this discussion, the Investigator judges that the subject's/subject's caregiver classification was incorrect, the Investigator will document it in a) the subject's medical notes with the rationale for the new classification, and b) the eCRF, documenting the new classification of the bleed according to the Investigator, and whether or not the subject's caregiver agreed with this new classification. With regard to those changes, the Investigator's classification of "spontaneous" or "traumatic" will be used (if different from the classification recorded in the eDiary by the subject/subject's caregiver).

Bleeding episodes will not be reported as AEs; however, the concomitant events associated with a bleed may be reported as an AE, if appropriate (i.e., a fracture in an elbow). Both spontaneous bleeding episodes and traumatic bleeding episodes will be collected.

The following information will also be documented in the eDiary:

- The type of bleeding episode (e.g., spontaneous, traumatic)
- The date the bleeding episode occurred
- The dose administered for the bleeding episode, including any repeat doses
- The location of the bleed (joint, internal, skin/mucosa, or muscle)
- The reason for administering the dose (medical or nonmedical reasons [e.g., strenuous activity or other reason])

7.1.4.2. Procedure to Treat the Bleeding Episode

The dose of rFIXFc to treat the bleeding episode will be based on the subject's clinical condition, known PK information from the previous study or FIX trough and/or peak (recovery) measurements in this study, type and severity of the bleeding event (see Appendix A for guidance on dosing), and input from the Sponsor, if necessary.

Subjects and subjects' 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. If a subject has one spontaneous bleed and the Investigator is concerned the trough level is too low, the Investigator should contact the Sponsor to discuss next steps for this subject.

- **If the bleeding episode stops with a single IV dose of rFIXFc,** the subject should return to his previous dosing regimen and will be treated with his next dose of rFIXFc, as previously scheduled, even if this results in consecutive daily doses.
- **If the bleeding episode does not stop within 48 hours with the single IV dose of rFIXFc,** the subject or the subject's caregiver should consult with the Investigator for an optimal rFIXFc dose and dosing interval. Because of the long lasting effect of

rFIXFc, it is recommended that the subject takes the first follow-up dose no less than 48 hours after the initial dose. However, if the subject experiences persistent pain or other signs of ongoing bleeding, the first follow-up dose may be administered before 48 hours. Administration of the second dose of rFIXFc as a follow-up treatment will be determined by the Investigator, based on the subject's clinical condition. Please refer to Appendix A for rFIXFc dosing guidance. Once the bleeding event stops, the subject will return to his previous dosing regimen and will be treated with his next dose of rFIXFc as previously scheduled, even if this results in consecutive daily doses.

- **If the bleeding event does not stop with 2 doses (initial and follow-up treatments) of rFIXFc,** the subject or the subject's caregiver should contact the Investigator for advice. Following consultation with the Investigator, a third dose of rFIXFc will be administered 48 hours after the administration of the second dose of rFIXFc. The third dose (second follow-up dose) may be at the same dose level as the second dose or a dose determined by the Investigator based on the subject's clinical condition. Please refer to Appendix A for rFIXFc dosing guidance. Once the bleeding event resolves, the subject will return to his previous dosing regimen and will be treated with his next dose of rFIXFc as previously scheduled, even if this results in consecutive daily doses.

- **If the bleeding event still has not stopped after 3 doses (initial and 2 follow-up doses) of rFIXFc**, the Investigator should contact the Sponsor Medical Monitor to discuss the next steps for treatment of the subject.

7.1.4.3. Dose and/or Interval Modification Following Bleeding Episodes

Dose and/or interval modification following bleeding episodes can occur if any subject experiences ≥2 spontaneous bleeding episodes over a consecutive 3-month period. The Investigator can adjust the rFIXFc dose, as follows:

- If an increase is required, the dose may be increased in increments of at least 5 IU/kg.

- The dose and/or interval may be adjusted after discussion with the Sponsor Medical Monitor.

See Section 5.3 for a description of regimen changes.

7.2. Overall Study Duration and Follow-Up

The study period will consist of Screening and Treatment. Subjects are expected to be followed through at least 100 exposure days (EDs) to rFIXFc and may further continue in this study for up to 4 years or until rFIXFc is commercially available in the applicable participating country.

7.2.1. Screening

Subject eligibility for the study will be determined prior to enrollment (Visit 1). The EOT Visit for the parent study may serve as Visit 1 for this study, however, if there is a gap of ≥37 days following the EOT Visit of the parent study, all laboratory assessments for Visit 1 must be performed and eligibility confirmed prior to dosing with rFIXFc.

Informed consent for the extension study may be reviewed and obtained during the EOT visit of the previous study, and if not, consent must be obtained at Visit 1 of the extension study.

7.2.2. Treatment

Eligible subjects will self-administer rFIXFc intravenously according to their assigned treatment regimen. Caregivers or Sponsor-approved designees may also administer rFIXFc. Where appropriate, rFIXFc may be administered in the clinic.

7.2.3. Follow-Up

A final study visit will be conducted approximately 14 (+7) days after treatment with the last dose of study drug rFIXFc. This 14 day follow-up visit is not required if a subject ends his participation in the extension study to enroll into another rFIXFc study.

7.3. Study Stopping Rules

The Sponsor may terminate this study at any time, after informing Investigators. Investigators will be notified by the Sponsor or designee if the study is placed on hold, completed, or closed.

The study must be stopped in the following cases:

- Three subjects develop a high titer (i.e. ≥5.00 BU/mL) inhibitor, as defined in Section 7.1.2. The number of subjects can be adjusted based on sample size when more subjects are included in this trial from other rFIXFc parent studies.

- An unexpected, serious, or unacceptable risk to the study subjects.

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 Sponsor's Safety Surveillance Team, it is determined that the study should be permanently discontinued, then subjects will attend a final visit.

7.4. End of Study

The end of study is when the last subject completes his last visit.

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 signing the informed consent at Visit 1 of the study, or at the EOT of the previous study. The eligibility assessment must be documented.

1. Ability to understand the purpose and risks of the study and ability to provide signed and dated informed consent and authorization to use protected health information (PHI) in accordance with national and local subject privacy regulations. Parental or guardian consent is required for subjects who are less than 18 years of age or unable to give consent, or as applicable per local laws. Subjects who are less than 18 years of age may provide assent in addition to the parental/guardian consent, if appropriate. Written informed consent must be provided before any screening tests or assessments are performed.

2. Subjects who have completed studies 998HB102, 9HB02PED, or other studies with rFIXFc.

8.2. Exclusion Criteria

Candidates will be excluded from study entry if any of the following exclusion criteria exist at the time of signing the informed consent at Visit 1 of the study, or at the EOT of the previous study:

1. Confirmed high-titer inhibitor (≥5.00 BU/mL), as defined in Section 7.1.2.

2. Current enrollment in any other clinical study.

3. Inability to comply with study requirements.

4. Other unspecified reasons that, in the opinion of the Investigator or Biogen Idec, make the subject unsuitable for enrollment.

9. ENROLLMENT AND REGISTRATION PROCEDURES

9.1. Enrollment and Screening

Adult subjects must provide written informed consent and pediatric subjects may provide written assent (as appropriate), before any screening tests or assessments are performed. For subjects less than 18 years of age, or, for subjects otherwise unable to provide written informed consent, parents or legal guardian(s) must obtain the informed consent form and return to the clinic following review to discuss and sign the Consent/Assent forms, as appropriate. At the time of consent/assent, the subject will be enrolled into the study. This will occur following successful completion of the EOT assessments for the previous rFIXFc study. Participating study sites are required to document all screened candidates initially considered for inclusion in this study. If a subject is excluded from the study, the reasons for exclusion will be documented in the subject's source documents and on the screening log.

9.2. Registration of Subjects

Subjects will be registered at Visit 1 after all assessments for the EOT Visit of the previous rFIXFc study have been completed and after the Investigator has verified that they are eligible per criteria in Sections 8.1 and 8.2. Subjects will retain their previous study identification number. Subject identification numbers previously assigned will not be reused for another subject even if a subject does not receive treatment.

Refer to the Study Reference Manual for details on registration.

As confirmation, the Sponsor or designee will provide the Investigator with written verification of the subject's registration by email or fax.

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 designated distributors.

Refer to Section 12 (Study Treatment Management) for specifics on the preparation, storage, handling, disposal, and accountability of study treatment.

10.1. Study Treatment Schedule and Administration

Instructions for preparation and administration of rFIXFc are provided in the Drug Handling and Administration (DHA) Manual.

rFIXFc will be administered over several minutes by slow intravenous (IV) injection. The rate of administration should be determined by the subject's comfort level. Any missed doses should be taken as soon as possible or per the instructions of the Investigator.

Subjects will follow either a weekly, individualized, or personalized prophylaxis or be treated on-demand based on the subject's clinical profile and by PK profiles and dosing levels from the parent rFIXFc study. Subjects 12 years of age or older will be permitted to change from prophylaxis regimens to on-demand treatment, and from on-demand treatment to prophylaxis during this study. Subjects less than 12 years of age will receive a prophylactic regimen and will not have the option to change to on-demand treatment until they reach the age of 12 years during the study.

All treatment regimen changes will be discussed between the Investigator and the subject (and parent/guardian, as applicable). All treatment regimen changes require the approval of the Sponsor Medical Monitor.

10.1.1. Prophylaxis Regimens

Prophylaxis treatment options may include weekly prophylaxis, individualized prophylaxis, or personalized prophylaxis. A weekly prophylaxis regimen is comprised of rFIXFc doses of 20 IU/kg to 100 IU/kg, administered once weekly. Subjects on an individualized prophylaxis regimen are treated at doses and dosing intervals that are tailored based on their PK profiles and dosing levels from parent rFIXFc studies or FIX trough and/or peak (recovery) levels obtained during this extension study. In pediatric subjects <12 years of age, the dose may be adjusted up to 100 IU/kg, with the interval decreased to twice weekly, if necessary to maintain adequate FIX activity trough levels and prevent spontaneous bleeding events..

The personalized prophylaxis dosing option will require approval from the Medical Monitor.

Please refer to Section 5.3.2 for descriptions of prophylaxis dosing options.

10.1.2. On-demand (Episodic) Treatment

The individual dose of rFIXFc to treat bleeding episodes will be based on the subject's clinical condition and the type and severity of the bleeding event. Please refer to Appendix A for on-demand dosing guidelines. Subjects less than 12 years of age entering from a parent rFIXFc study will not have the option of an on-demand treatment until they reach the age of 12 years during the study.

10.1.3. Surgery

For subjects who require emergent or elective surgery during the study period, the dose and regimen of rFIXFc shall be that deemed appropriate for the type of surgery to be performed.

All major surgeries must take place in a center that can provide study treatment, trained study personnel, post-operative assessments, and hematological consultations by the Investigator or Sub-Investigator. If the surgery does not occur 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 trial and/or a separate agreement has been executed, permitting the use of study drug and Biogen Idec's rights to data generated in the trial at an alternative Institution deemed appropriate by the Investigator.

2. The Investigator and/or appropriate qualified/licensed delegate is available to:
    a. Administer all the rFIXFc doses required during surgery and during post-operative rehabilitation (if applicable).
    b. Provide medical oversight and guidance throughout the duration of the pre-operative and the intra-operative periods.

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

- Major surgery is defined as any surgical procedure (elective or emergent) that usually, but not always, involves general anesthesia and/or respiratory assistance, in which a major body cavity is penetrated and exposed, or a substantial impairment of physical or physiological functions is produced (e.g., laparotomy, thoracotomy, craniotomy, joint replacement, or limb amputation).

- Minor surgery is defined as any surgical procedure (elective or emergent) that does not involve general anesthesia and/or respiratory assistance (e.g., minor dental extractions, incision, and drainage of abscess, joint or other injections, or simple excisions).

All major surgeries will be reported as SAEs.

For major surgery, inhibitor and anti-factor rFIXFc antibody testing should be performed 2 to 4 weeks prior to the scheduled surgery, pre-operatively on the day of surgery, 1-2 weeks post-surgery (Visit 3), and at the last post-operative visit (Visit 4). Visit 4 (Last Post-Operative Visit) occurs when the subject returns to a regular rFIXFc regimen, as determined by the Investigator, and is required only if the subject did not return to a regular rFIXFc regimen at Visit 3. For minor surgery, the testing may be performed at the Investigator's discretion.

On the day of surgery, subjects will be given a preoperative dose of rFIXFc as a bolus, and, in the case of emergency surgery, as soon as possible prior to the procedure. Pre-dose FIX activity levels will be sampled, followed by FIX peak (recovery) samples, 30 (±5) minutes post-dosing. A repeat sample may be taken approximately 6 to 9 hours after the loading preoperative dose is administered or at an interval based on the local standard of care for determination of subsequent rFIXFc dosing. During the subject's hospitalization, FIX activity will be measured daily at the local laboratory and a plasma aliquot will be prepared for each blood sample drawn so that subsequent analysis at the central laboratory can be performed.

Doses higher than 100 IU/kg may be used in the context of surgery to achieve the required FIX levels to prevent bleeding. However, the maximum number of daily or every-other-day doses will not exceed the predicted accumulated C_{max} of approximately 150% of normal (normal ranges are 50% to 150% FIX activity). All surgical dosing plans will be discussed with and approved by the Sponsor Medical Monitor before surgery. All doses administered in the hospital will be captured in the eCRF.

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

10.2. Treatment Precautions

Precautions should be taken with any FIX product.

The subject will be provided with specific instructions on what to do in the event of an overdose, allergic reaction, bronchospasm, or anaphylaxis while at home, including how to seek emergency medical treatment.

10.3. Modification of Dose and/or Treatment Schedule

10.3.1. Prophylaxis Regimen

Please refer to Section 5.3.2 for details on prophylaxis regimens.

10.3.2. On-demand (Episodic) Treatment

rFIXFc doses to treat bleeding episodes will be based on the subject's clinical condition, the type and severity of the bleeding episode, and in some cases, FIX peak (recovery) levels. A subject's PK profile and dosing levels from his parent study may also be used to guide dosing decisions.

Specific guidance for treatment of bleeding episodes is presented in Appendix A.

10.4. Treatment Compliance

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

Subjects will record both routine doses and doses for the treatment of bleeding episodes in the eDiary. Diary data will be reviewed on a regular basis by site staff.

10.5. Concomitant Therapy and Procedures

10.5.1. Concomitant Therapy

A concomitant therapy is any drug or substance administered from 30 days prior to Visit 1 until 14 (+7) days after the last dose of rFIXFc in this extension study. Concomitant medications, procedures, or therapies must be recorded on the subject's eCRF, according to the instructions for eCRF completion. Adverse events (AEs) related to administration of these therapies or procedures must be documented on the appropriate eCRF.

10.5.1.1. Allowed Concomitant Therapy

Therapy considered necessary for the subject's welfare may be given at the discretion of the Investigator.

Allowed therapies include treatment for hepatitis and/or HIV, routine immunizations, treatment with systemic steroids and/or inhaled steroids (with approval of the Sponsor Medical Monitor), and/or non-steroidal anti-inflammatory drugs (NSAIDs). Acetylsalicylic acid is permitted only at a low dose (≤81 mg), with approval of the Sponsor Medical Monitor.

All allowed therapies must be recorded in the eCRF.

10.5.1.2. Disallowed Concomitant Therapy

No other investigational drug may be used concomitantly with the study treatment.

The following concomitant medications are not permitted during the study:

- Acetylsalicylic acid doses >81 mg.
- Current systemic treatment with chemotherapy and/or other immunosuppressant drugs (unless advised otherwise after consult with the Medical Monitor)
- Any other FIX product (with exceptions listed in Section 11.1)

10.5.2. 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 between the time the subject is enrolled in the study until the study is completed/terminated by the Sponsor, unless the subject is being followed for study-related toxicity.

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

10.6. Continuation of Treatment

Subjects are expected to be followed through at least 100 exposure days (EDs) to rFIXFc and may further continue in this study for up to 4 years or until rFIXFc is commercially available in the applicable participating country.

11. WITHDRAWAL OF SUBJECTS FROM STUDY TREATMENT AND/OR THE STUDY

11.1. Discontinuation of Study Treatment

A subject *must* permanently discontinue rFIXFc for any of the following reasons:

- A Grade 2 or greater allergic drug reaction in association with administration of rFIXFc, as defined below by the Recommendations for Grading of Acute and Sub-Acute Toxic Effects on the World Health Organization (WHO) scale [WHO handbook, 1979]:
    - Grade 2 Bronchospasm related to rFIXFc; no parenteral therapy needed
    - Grade 3 Bronchospasm related to rFIXFc; parenteral therapy required
    - Grade 4 Anaphylaxis related to rFIXFc
- A high-titer inhibitor (≥5.00 BU/mL), as defined in Section 7.1.2.
- Use of FIX products other than rFIXFc, unless it occurs in one life-threatening emergency and/or as a result of one accidental use, and the Sponsor agrees to retain the subject in the study. Use must be recorded in the subject's eDiary and eCRF and the Investigator should contact the Sponsor Medical Monitor.
- Any condition a subject develops that precludes him from complying with the study procedures.
- The subject experiences a medical emergency that necessitates discontinuation of treatment.
- Clinical 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 or legal guardian can withdraw the subject from the study at will at any time.
- The subject and/or his parent/guardian withdraw consent.
- At the discretion of the Investigator or Sponsor for noncompliance.

The reason for discontinuation of study treatment must be recorded in the subject's eCRF.

For any subject who no longer responds to treatment with rFIXFc, as determined by the Investigator, a decision will be made with the Sponsor whether to continue the subject on the study.

Subjects who discontinue treatment should remain in the study to complete protocol-required tests and assessments, and then must be permanently withdrawn from the study.

11.2. Withdrawal of Subjects From Study

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

- The subject and/or parent/guardian withdraw consent.
- The subject and/or parent/guardian are unwilling or unable to comply with the protocol
- The subject meets any of the criteria defined in Section 11.1.

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

Subjects who discontinue study treatment and are withdrawn from the study will not be replaced.

If the decision is made to withdraw the subject from the study, the final study visit/early termination visit will be performed, as described in Section 4 (Table 1).

12. STUDY TREATMENT MANAGEMENT

Please refer to the Directions for Handling and Administration (DHA) for full details regarding rFIXFc.

The study treatment must be stored in a secure location. Accountability for study treatment is the responsibility of the Investigator. More details concerning this responsibility are included in Section 12.1.4. Study treatment must only be dispensed by designated study staff. Study treatment is to be dispensed only to subjects, to parents/legal guardians of subjects enrolled in this study, or to Sponsor-approved designees. Once study treatment is dispensed to a subject, it can only be administered to that subject. Study treatment vials are for one-time use only; any study treatment remaining in the vial should not be used for another subject.

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 the study treatment. **The DHA supersedes all other references (e.g., Investigator's Brochure).**

The subject or the subject's caregiver must return to the investigational site for dispensation of rFIXFc and administration supplies before the earliest expiration date of drug in the subject's inventory. This is to ensure that adequate drug supplies for treatment are maintained, including an adequate supply to treat breakthrough bleeding or due to delays in scheduling clinic visits.

12.1. rFIXFc (BIIB029)

rFIXFc is supplied in a kit that contains several components: a vial of lyophilized drug, the diluent syringe, a filter device vial adapter, and a winged injection set. The lyophilized powder is in a clear glass vial containing 250, 500, 1000, 2000, or 3000 IU of rFIXFc (nominal strengths). Not all strengths may be available at the start of the study. The drug product is reconstituted with a diluent syringe containing 5 mL of [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 concentrations of excipients for the 3000 IU/vial strength are [redacted] L-histidine, [redacted] sucrose, [redacted] mannitol, [redacted] polysorbate 20, and [redacted] sodium chloride.

The label will be compliant with local labeling requirements.

12.1.1. rFIXFc Preparation

The individual preparing rFIXFc should first carefully review the instructions provided in the DHA (if site staff), or in subject information materials provided by the site.

If the packaging is damaged, or if there is anything unusual about the appearance or attributes of the vials or drug, it should not be used. The vial in question should be saved by the subject or site, and then immediately reported by the site to the Sponsor.

12.1.2. rFIXFc Storage

Site stocks of rFIXFc kits should be stored at 2°C to 8°C in a monitored, locked refrigerator with limited access or the room in which the refrigerator resides must be locked and have limited access.

12.1.3. rFIXFc Handling and Disposal

The Investigator must return all unused vials/kits of rFIXFc as instructed by the Sponsor. The instructions for return will be provided to the site at the time the request is made by the Sponsor.

If the Sponsor requires the study site to destroy unused rFIXFc kits, the institution/Principal Investigator(s) must notify the Sponsor, in writing, of the method of destruction, the date of destruction, and the location of destruction.

12.1.4. rFIXFc Accountability

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.

The subject or the subject's caregiver 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 rFIXFc supplied, dispensed, and subsequently returned to the Sponsor. A written explanation must be provided for any discrepancies.

13. EFFICACY ASSESSMENTS

Subjects that enroll into this study will be assessed only for those parameters that had been previously assessed in the parent study.

13.1. Clinical Efficacy Assessments

The following clinical tests/assessments will be performed to assess the efficacy of rFIXFc.

For all subjects:

- Number of bleeding episodes reported by each subject or the subject's caregiver during the study period
    - Recording of bleeding episodes in the hospital in the eCRF by the Surgeon/Investigator; recording of all other bleeding episodes in the eDiary by the subject or subject's caregiver
- Dose and dosing interval adjustments
- Assessment of response to treatment using a 4-point scale in the eDiary (Appendix C)
    - Assessment of response to bleeding episodes using a 4-point scale by the Investigator for individual bleeding episodes treated in the clinic; assessment of all other bleeding episodes in the eDiary by the subject or subject's caregiver
- Physician's global assessment of response to the subject's treatment regimen using a 4-point scale (Appendix D)

For subjects undergoing surgery, in addition to the above

- Investigator/Surgeon assessment of hemostatic response using the 4-point bleeding response scale (Appendix E)
- Number of injections and dose per injection to maintain hemostasis during the surgical period
- Number of blood product units transfused during surgery
- Estimated blood loss (mL) during surgery and the post-operative period

Refer to Section 4 for the timing of assessments.

13.2. Laboratory Efficacy Assessments

The following laboratory tests/assessments will be performed to assess the efficacy of rFIXFc:

- FIX activity, peak (recovery) and/or trough measurements, if applicable (determined by the one-stage aPTT clotting assay performed at the central laboratory)

Refer to Section 4 for the timing of assessments.

13.3. Pharmacokinetic Assessments

Not applicable.

13.4. Pharmacodynamic Assessments

Not applicable.

13.5. Additional Assessments

In addition to the efficacy assessments above, the following tests will be performed.

13.5.1. Hemophilia Joint Health Score

Joint assessment will be conducted at Visit 1 using a modified Hemophilia Joint Health Score (HJHS) for adult subjects. This assessment is based on the scoring system used in a joint scoring reliability study in boys with hemophilia [Hilliard 2006]. It has been used as a tool to evaluate musculoskeletal outcomes in a cohort of 20 boys, aged 4 to 17 years [Saulyte Trakeymieine 2010]. Modifications were included to adapt the HJHS scoring system to an adult hemophilia population and according to comments in a recent validation study by the International Hemophilia Prophylaxis Study Group [Feldman 2011].

Pediatric subjects will continue to use the HJHS, Version 2.1, and a joint assessment will be conducted at Visit 1. Version 2.1 was published as an appendix to a validation study of Version 1.0 [Feldman 2011].

Subjects from other parent studies will continue to use the joint health assessment instrument used in parent study.

Joint health assessments will only be performed if they were conducted during the parent study.

13.5.2. Patient-Reported and Health Outcomes

Only patient-reported outcomes that were completed during the parent study should be completed during the current study. If a subject goes outside of the age range for a questionnaire, he should no longer complete it. The following patient-reported outcome assessments will be performed, if applicable, for all subjects every 6 months, where linguistic validations exist in which the subject and/or parent/guardian is fluent. For pediatric subjects,

caregivers will perform these assessments, as appropriate. The Investigator will administer the following age-appropriate questionnaires at the appropriate visits.

- Haem-A-QoL [von Mackensen & Gringeri 2009]
- Haemo-QoL [von Mackensen 2004]
- Hemo-Sat-Patient Satisfaction Scale for parent/guardian, Version 15 [MAPI Research Institute 2009]
- CHO-KLAT [CHO-KLAT 2009]
    - Children Version 2.0 (for children previously enrolled in study 9HB02PED who are less than 18 years of age).
    - Proxy, Version 2.0p (for parent/guardian of children who were previously enrolled in study 9HB02PED and who are less than 18 years of age)
- EQ-5D-Y [EQ-5D-Y 2011]
- EQ-5D-3L [EuroQol 1990]

Other patient-reported health outcomes related to hemophilia that are assessed include:

- Number of hospitalizations, excluding pre-planned hospitalizations, elective surgery documented at Visit 1, and emergent surgery
- Number of emergency room visits
- Number of physician visits excluding study visits
- Number of hospitalization days
- Number of days off work, school/daycare, or preschool
- Number of days off work for a parent/guardian

13.5.3. Optional Laboratory Assessment

For subjects who give their consent (or whose parent/guardian gives consent for pediatric subjects), a sample of blood will be collected during the study to conduct an analysis of genetic risk factors in the hemophilia B patient population. This exploratory laboratory assessment consists of DNA testing with full genome sequence.

13.5.4. Archive Plasma Samples

Samples for FIX inhibitor testing will be collected for each subject, at each visit, for back-up and archiving. Samples will be archived for testing (if required) for immunology, further coagulation assays, or for clarification of any clinical or laboratory AE.

14. SAFETY ASSESSMENTS

Subjects that enroll into this study will be assessed only for those parameters that had been previously assessed in the parent study.

14.1. Clinical Safety Assessments

The following clinical assessments will be performed to assess the safety profile of rFIXFc:

- Physical examination
- Vital signs (blood pressure, pulse, respiratory rate, and temperature [°C])
- Medical and surgical history (from previous study and updated)
- Height
- Weight
- Concomitant therapy and procedures
- AEs and SAEs

Refer to Section 4 for the timing of assessments.

14.2. Laboratory Safety Assessments

The following laboratory tests will be performed by the central laboratory to assess the safety profile of rFIXFc:

- Hematology: White blood cell count (WBC), differential, platelet count, hemoglobin, hematocrit
- Blood chemistry: sodium, potassium, chloride, glucose, total protein, total bilirubin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), blood urea nitrogen (BUN), and serum creatinine.
- Nijmegen-modified Bethesda assay for development of inhibitors
- Refer to Section 4 for the timing of assessments.

15. SAFETY DEFINITIONS, MONITORING, AND REPORTING

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

At the signing of the informed consent form (ICF), each subject must be given the names and telephone numbers of study site staff for reporting AEs and medical emergencies.

15.1. Definitions

15.1.1. Serious Pretreatment Event

The term "serious pretreatment event" is not applicable in this extension study as all AEs occurring up to the time of subject consent in this study will be captured as part of the subject's previous study records.

15.1.2. Adverse Event

An AE is any untoward medical occurrence in a patient or clinical investigation subject who has been administered a pharmaceutical product and who 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 it is related to the medicinal (investigational) product.

Bleeds in this patient population are generally not considered AEs. Bleeding episodes that meet any criteria of "serious" (Section 15.1.3) should be reported as SAEs. All bleeding episodes will be captured in the eDiary maintained by the subject throughout the study period.

15.1.3. 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
- results in a congenital anomaly/birth defect

All major surgeries will be reported as SAEs. 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).

15.2. Monitoring and Recording Events

15.2.1. Serious Pretreatment Events

A serious pretreatment event is not applicable in this extension study as all AEs occurring up to subject consent in this study will be captured as part of the subject's previous study records.

15.2.2. Adverse Events

Any AE experienced by the subject during participation in this extension study is to be recorded on the eCRF, regardless of the severity of the event or its relationship to the study treatment.

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

15.2.3. Serious Adverse Events

Any SAE experienced by the subject between the day of signing the ICF and the last study follow-up visit/telephone call is to be recorded on an SAE Form and eCRF, regardless of the severity of the event or its relationship to study treatment. Serious adverse events that occur up to 21 days after the subject's last dose of rFIXFc must also be recorded on the SAE Form and eCRF. Serious adverse events must be reported to Quintiles and to designated personnel, as detailed in the study file.

Any SAE that is 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.

Subjects will be followed for all SAEs until the last study follow-up visit/telephone call. Thereafter, the event should only be recorded if the Investigator considers it related to study treatment.

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 7.1.2.

- A Grade 2 or greater allergic drug reaction in association with administration of rFIXFc, as defined below by the Recommendations for Grading of Acute and Sub-Acute Toxic Effects on the WHO scale [WHO handbook 1979]:
    - Grade 2 Bronchospasm related to rFIXFc; no parenteral therapy needed
    - Grade 3 Bronchospasm related to rFIXFc; parenteral therapy required
    - Grade 4 Anaphylaxis related to rFIXFc
- A subject develops a vascular thrombotic event in association with the administration of rFIXFc, with the exception of IV injection site thrombophlebitis.

All major surgeries will be reported as SAEs.

Subjects will be informed of early symptoms and signs of thrombotic phenomena, including pain and/or tenderness along a vein, 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 subject should be instructed to seek immediate medical care.

15.2.4. All Events

All events must be assessed to determine the following:

- If the event meets the criteria for an SAE as defined in Section 15.1.3
- The relationship of the event to study treatment as defined in Section 15.3.1
- The severity of the event as defined in Section 15.3.2

15.2.5. 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 the subject has signed the ICF and up to 21days after the final dose of study treatment must be reported to Quintiles Pharmacovigilance within 24 hours of the study site staff becoming aware of the event.

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 the 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 the following:

Fax: Please fax to Quintiles Pharmacovigilance at the country-specific fax number provided in the Study Manual.

15.2.5.1. Deaths

Death is an outcome of an event. The event that resulted in death should be recorded and reported on the appropriate eCRF. All causes of death must be reported as SAEs. The Investigator should make every effort to obtain and send death certificates and autopsy reports to Quintiles Pharmacovigilance.

15.3. Safety Classifications

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

15.3.2. Severity of Events

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

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

15.3.3. Expectedness of Events

Expectedness of all AEs will be determined according to the Investigator's Brochure for rFIXFc.

15.4. Procedures for Handling Special Situations

15.4.1. Overdose

An overdose is any single dose of study treatment given to a subject or taken by a subject that exceeds the maximum dose described in the protocol, 150 IU/kg. All overdoses should be recorded on an Overdose Form and faxed to Quintiles Pharmacovigilance within 24 hours. An overdose should be reported even if it does not result in an AE. Overdoses do not need to be recorded in the eCRF; dosing information is recorded in the eCRF.

15.4.2. Medical Emergency

In a medical emergency requiring immediate attention, study site staff will apply appropriate medical intervention, according to current standards of care. The Investigator should contact the Sponsor Medical Director for this study, Baisong Mei at +1-857-928-3348 (mobile) or Geoffrey Allen, MD at +1-781-558-0857 (mobile).

15.4.3. 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 when study drug-exposed conception occurs.

15.4.4. Regulatory Reporting

Suspected Unexpected Serious Adverse Reactions (SUSARs) are SAEs that are unexpected and judged by the Investigator or the Sponsor to be related to the study treatment administered.

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

15.5. 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.
- Report congenital abnormalities/birth defects in the offspring of male subjects when study drug-exposed conception occurs.

- Complete an SAE form for each serious event and fax it to Quintiles Pharmacovigilance within 24 hours of the study site staff becoming aware of the event.

- Pursue SAE follow-up information actively and persistently. Follow-up information must be reported to Quintiles Pharmacovigilance within 24 hours of the study site staff becoming aware of new information.

- Ensure all AE and SAE reports are supported by documentation in the subjects' medical records.

- Report SAEs to local ethics committees, as required by local law.

15.6. Biogen Idec Responsibilities

Biogen Idec's responsibilities include the following:

- Before study site activation and subject enrollment, the Clinical Monitor or Sponsor 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.

- Biogen Idec 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, subjects who enroll into study 9HB01EXT from any rFIXFc parent study will have their parent study data integrated with their data from 9HB01EXT. A parent study is defined as a study where subjects may be enrolled into 9HB01EXT after study completion or at a time specified in the protocol. .

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 number, mean, median, standard deviation, minimum and maximum, and, where appropriate, with the 25th and 75th percentiles. Categorical variables will be summarized by the number and percentage in each category.

16.1. Description of Objectives

16.1.1. Primary Objective

See Section 6.1.1 for the study's primary objective.

16.1.2. Secondary Objective

See Section 6.1.2 for the study's secondary objective.

16.2. Description of Endpoints

16.2.1. Primary Endpoint

See Section 6.2.1 for the study's primary endpoint.

16.2.2. Secondary Endpoint

See Sections 6.2.2 and 6.2.3 for a listing of the study's secondary endpoint.

16.3. Demography and Baseline Disease Characteristics

The analysis of demography and baseline disease characteristics will be based on the Safety Analysis Set. The Safety Analysis Set includes all subjects who have received at least one dose of rFIXFc, as described in Section 16.6.1 .

Demographic and baseline disease characteristics will be summarized categorically and/or with descriptive statistics, as appropriate, using the data at the entry into the parent studies. Demographic data to be tabulated includes age, race, hemophilia history, genotype, and other disease-specific measures.

Baseline disease characteristics, based on general medical and surgical, hemophilia, and bleeding histories, will be summarized by 9HB01EXT treatment regimen and overall, 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 genotype and other disease- and treatment-specific measures.

16.4. Efficacy

16.4.1. Analysis Population

All subjects who consent to participate in 9HB01EXT will be included in the All-enrolled Analysis Set.

Subjects who receive at least 1 dose of rFIXFc will be included in the Full Analysis Set (FAS). Efficacy analyses will be based on the FAS.

16.4.2. General Methods of Analysis

All efficacy endpoints are secondary. No imputation will be applied to any missing efficacy data. The periods in which data will be used for efficacy and surgical rehabilitation analyses will be defined in the statistical analysis plan. 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 they occurred during the efficacy period. However, if a visit is coincidental with a surgical/rehabilitation period for a major surgery, it will be excluded from the analysis.

16.4.3. Endpoint Analysis

16.4.3.1. Annualized Bleeding Episodes and Annualized rFIXFc Consumption

Bleeding episodes will be annualized for each subject first, and then summarized and tabulated by treatment arm, treatment regimen, or age cohort, as appropriate, for the parent studies and the treatment regimen in Study 9HB01EXT. These analyses will also be performed for each type of bleed (spontaneous, and traumatic). Summaries of these data will be based on the FAS.

16.4.3.2. Other Efficacy Endpoints

The response to treatment for bleeding will be summarized by the number and percentage of bleeding episodes for each response (excellent, good, moderate, none). These data will be summarized overall during each study based on the FAS.

16.4.3.3. Surgery Endpoints

Analysis of surgery endpoints will be performed for subjects who had surgeries during the study, either emergently or electively. Summary statistics of major surgery endpoints will be provided for the surgical/rehabilitation period.

16.4.4. Additional/Exploratory Analysis

The number of injections and the 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 overall average across all bleeding episodes for a given subject. These data will be summarized overall and for subgroups of interest during each study based on the FAS. Other efficacy analyses can be conducted for exploratory purposes.

16.5. Patient-Reported and Health Outcomes

16.5.1. Analysis Population

The FAS will be used for the analysis of patient-reported and health outcomes.

16.5.2. Methods of Analysis

16.5.2.1. Patient-Reported Outcomes

Questionnaires for patient-reported outcomes are described in Section 13.5.2.

Endpoints for patient-reported outcomes (Haem-A-QoL, Haemo-QoL, Hemo-Sat-P, CHO--KLAT Children, CHO--KLAT Proxy, EQ-5D-Y, and EQ-5D-3L) will be analyzed in a separate report. These endpoints will be analyzed by summarizing actual values and change from baseline, as appropriate.

16.5.2.2. Health Outcomes

Summary statistics of health outcome endpoints will be tabulated at each data collection timepoint.

16.6. Safety

16.6.1. Analysis Population

Subjects who receive at least one dose of rFIXFc will be included in the Safety Analysis Set.

16.6.2. Methods of Analysis

For the analysis of safety, data in 9HB01EXT will be integrated with the parent study data, unless specified otherwise. The incidence of AEs will be tabulated overall, by severity, and by relationship to treatment. In addition, the incidence of AEs will be presented by exposure day (ED) intervals. An ED is a 24-hour period, in which one or more rFIXFc injections are given.

Subject listings will be provided for all AEs, SAEs, AEs resulting in discontinuation of the study treatment or withdrawal from the study, and death. Findings for clinical lab values will be summarized by descriptive statistics. Listings of vital signs and abnormal laboratory test results will be provided.

The total number of EDs of rFIXFc will be summarized by treatment regimen and overall for 9HB01EXT, and overall using combined data from the parent studies and 9HB01EXT.

16.7. Inhibitor Formation Data

16.7.1. Analysis Population

The Safety Population (as defined in Section 16.6.1) will be the basis for analyses of inhibitor formation.

16.7.2. Methods of Analysis

The proportion of subjects with an inhibitor during rFIXFc administration will be provided with the exact (Clopper-Pearson) 2-sided, 95% confidence interval. Any subject with an inhibitor (as defined in section 7.1.2) following the initial rFIXFc administration, will be counted in the numerator; however, only subjects who have completed at least 50 EDs, and 100 EDs from their initial rFIXFc administration, will be included in the denominator. Unless all subjects complete at least 50 EDs, the proportion of subjects with an inhibitor will also be calculated using all subjects, regardless of the amount of exposure to rFIXFc, in the denominator.

16.8. Optional Laboratory Assessments

DNA testing with full genome sequence data may be performed to evaluate genetic risk factors in the hemophilia B patient population. The analysis, however, will be in a separate report and will not be included as part of any Clinical Study Report (CSR) or interim CSR of 9HB01EXT.

16.9. Interim Analyses

Interim analyses will be conducted during the study, as needed. Analyses will be descriptive in nature. No formal comparisons are planned and no hypotheses will be formally tested.

Due to the open-label nature of this study, personnel involved in conducting the interim analyses will have access to treatment assignments.

16.10. Sample Size Considerations

This is an extension study. Sample size is based on the planned sample sizes of Studies 998HB102 (N=100), 9HB02PED (N=20), and may be increased based upon subject participation in other rFIXFc parent studies.

17. ETHICAL REQUIREMENTS

The Sponsor and the Investigator must comply with all instructions, regulations, and agreements in this protocol and applicable International Conference on Harmonisation (ICH) and Good Clinical Practice (GCP) guidelines and conduct the study according to local regulations.

17.1. Declaration of Helsinki

The Investigator and Sponsor must adhere to the principles set forth by the Declaration of Helsinki, dated October 2008.

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.

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

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

The Sponsor 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 the Sponsor.

17.3. Subject Information and Consent

Prior to performing any study-related activities under this protocol, including screening tests and assessments, written informed consent with the approved ICF must be obtained from the subject or subject's legally authorized representative, as applicable, in accordance with local practice and regulations. Written informed consent must be obtained from all subjects participating in a clinical study conducted by the Sponsor.

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. The subject must be given sufficient time to consider whether to participate in the study.

A copy of the ICF, signed and dated by the subject, must be given to the subject. Confirmation of a subject's informed consent must also be documented in the subject's medical record prior to any testing under this protocol, including screening tests and assessments.

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

The signed consent form will be retained with the study records.

For subjects who are under 18 years of age (or legally a minor per local regulations), or who are otherwise unable to provide written informed consent, a parental/guardian consent will be obtained, the contents of which will be identical to that of the standard adult consent. Written subject assent will also be obtained from those subjects who are able to read and understand the assent form, a brief summary of the study process, benefits, and risks.

17.4. Subject Data Protection

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

The subject will not be identified by name in the eCRF or in any study report, and these reports will be used for research purposes only. The Sponsor, 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

The Sponsor 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 the Sponsor) with the subject before the subject makes a decision to participate in the study.

17.7. Registration of Study and Disclosure of Study Results

The Sponsor 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 the Sponsor or designee. This initiation visit will include a detailed review of the protocol and study procedures.

18.2. Study Supplies

The Sponsor will supply the rFIXFc while subjects participate in this study (see Section 12). Since study subjects will be required to maintain accurate records of each dose of rFIXFc administered during the study, the Sponsor will provide personal eDiaries to the study sites for subjects to use to record study information.

18.3. Quality Assurance

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

18.4. Monitoring of the Study

The Principal Investigator(s) 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 course of 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.

Downloads from the subjects' eDiaries described in Section 19.1.3 will be used as source data.

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.

18.5. Study Funding

The Sponsor will pay the clinic or institution where the study is conducted for the costs of running the study. All financial details are provided in the separate contract(s) between the Institution/Investigator and Sponsor.

18.6. 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, and management of SAE reports and data management. Before subjects are screened at each study site, the CRO will review study responsibilities with the Investigators and other study site staff, as appropriate.

19.1.2. Interactive Voice/Web Response System

Interactive Voice and Web Response System (IXRS) will be used in this study. Before subjects are screened or enrolled, the IXRS vendor will provide each study site with appropriate training and a user 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 (EDC) tool (eDiary) developed and supported by the EDC vendor and configured by the Sponsor.

Data entered by subjects using the eDiary will be downloaded to the database.

19.1.4. Central Laboratories for Laboratory Assessments

Central laboratories have been selected by the Sponsor to analyze all hematology, blood chemistry, inhibitor, and antibody samples collected for this study. Specifics regarding the requirements for laboratory specimen collection, handling, and analysis are provided in the study Laboratory Manuals, which are part of the Study Manual.

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

19.3. 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.

19.4. 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 Biogen Idec in writing and receive written authorization from Biogen Idec to destroy study records. In addition, the Investigator must notify Biogen Idec 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.

19.5. Study Report Signatory

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

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

20. REFERENCES

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21. SIGNED AGREEMENT OF THE STUDY PROTOCOL

I have read the foregoing protocol, "An Open-Label, Multicenter, Evaluation of the Long-Term Safety and Efficacy of Recombinant Human Coagulation Factor IX Fusion Protein (rFIXFc) in the Prevention and Treatment of Bleeding Episodes in Previously Treated Subjects with Hemophilia B," Version 4, and agree to conduct the study according to the protocol and the applicable ICH guidelines and GCP regulations, and to inform all who assist me in the conduct of this study of their responsibilities and obligations.

_____

Investigator's Signature Date

_____

Investigator's Name (Print)

_____

Study Site (Print)

APPENDIX A. rFIXFc DOSING GUIDELINE FOR TREATMENT OF BLEEDING EPISODES

The following table provides guidance for dosing with rFIXFc for bleeding episodes. Subjects should consult with the Investigator for an optimal rFIXFc level and dosing frequency. Because of the long lasting effect of rFIXFc, it is recommended that the subject take the first follow-up dose no less than 48 hours after the initial dose. However, if the subject experiences persistent pain or other signs of ongoing bleeding, the first follow-up dose may be administered before 48 hours. For major bleeding episodes the subjects will be instructed to administer treatment and contact the study staff as soon as possible.

Table 3: Dosing Guidelines for rFIXFc Therapy in Hemophilia B

Type of Hemorrhage	Factor IX Level Required (%)
Minor	
Epistaxis	20-30
Hemarthroses, uncomplicated	20-30
Superficial muscular	20-30
Superficial soft tissue	20-30
Moderate	
Epistaxis	25-50
Intramuscular with dissection	25-50
Soft tissue with dissection	25-50
Mucous membranes	25-50
Dental extractions	25-50
Hematuria	25-50
Hemarthroses, with limited motion	40-80
Major	
Epistaxis	50-100
Pharynx	50-100
Retropharynx	50-100
Retroperitoneum	50-100
Surgery	50-100
Central Nervous System (CNS)	50-100

APPENDIX B. HEMOPHILIA JOINT HEALTH SCORE (HJHS)

Appendix B1: Modified HJHS for Subjects Transferring from Study 998HB102

This modified HJHS is based on the scoring system used in a joint scoring reliability study in boys with hemophilia [Hilliard 2006].The modifications were done to adapt the scoring system to an adult hemophilia population and according to comments in a recent validation study by the international hemophilia prophylaxis study group [Feldman 2011].This version is for use only with subjects who were previously enrolled in study 998HB102.

Six joints (left ankle-LA, right ankle-RA, left elbow-LE, right elbow-RE, left knee-LK, right knee-RK) will be scored on a scale from 0 to 19 according to the following criteria: swelling, duration, muscle atrophy, crepitus, flexion loss, extension loss, instability, joint pain, and strength. Gait will be scored on a scale from 0 to 2 based on walking and climbing stairs. The total score will be the sum of scores from all 6 joints plus the gait score (range from 0 to 116 with 0 being normal and 116 being the most severe disease).

SCORING DETAILS

1. **Joint scoring will be done separately for the 6 joints (LA, RA, LE, RE, LK, RK) according to these categories and scales (range is 0-19 for each joint and 0-114 for all six joints):**

   Swelling

   0=none

   1=mild

   2=moderate

   3= severe

   Duration of swelling

   0=no swelling or ≤6 months

   1= >6 months

   Muscle atrophy

   0=none

   1=mild

2=severe

Crepitus on motion

0=absent

1=present

Flexion loss (includes plantarflexion of ankles)

0=none*

1=mild*

2=moderate*

3=severe*

Extension loss (includes dorsiflexion of ankles)

0=none*

1=mild*

2=moderate*

3=severe*

*Use the following as guidance for scoring flexion loss and extension loss at knees and elbows:

None: approximately 0-5 degrees

Mild: approximately 5-10 degrees

Moderate: approximately 11-20 degrees

Severe: approximately >20 degrees

Instability

0=none

1=significant pathologic joint laxity

Joint pain

0=no pain (either through range or at end range of motion)

1=present

Strength

0=normal (holds position against gravity and maximum resistance)

1=minimal decrease (holds position against gravity and moderate resistance, but not maximum resistance)

2=mild decrease (holds position against gravity or minimal resistance)

3=moderate decrease (able to move joint if gravity eliminated)

4=severe decrease (trace or no muscle contraction)

2. Gait will be scored once (range is 0-2):

0=No difficulty with walking or climbing up/down stairs

1=No difficulty with walking, but difficulty with stairs

2=Difficulty with walking and with stairs

Total score = sum of all joint scores plus the gait score (range is 0-116)

Appendix B2. HJHS Version 2.1 for All Other Subjects

All subjects from rFIXFc parent studies that were evaluated with HJHS Version 2.1 (Hemophilia Joint Health Score, Version 2.1, 2011) will continue to use this score.

APPENDIX C. SUBJECT'S ASSESSMENT OF RESPONSE TO TREATMENT OF BLEEDING

Using the eDiary, each subject or the subject's caregiver will rate the treatment response to any bleeding episode using the following 4-point scale (excellent, good, moderate, or none). This assessment is to be made approximately 8 to 12 hours from the time the injection was given to treat the bleeding episode and prior to any additional doses of rFIXFc given for the same bleeding episode. In this study, a bleed 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 treatment for the bleed, within which any symptoms of bleeding at the same location, or injections less than or equal to 72 hours apart, are considered the same bleed. Any injection to treat the bleed, taken more than 72 hours after the preceding one, will be considered the first injection to treat a new bleed at the same location. Response could also be assessed by the Physician for those subjects who were treated in the clinic or in the hospital with rFIXFc for bleeds or post-surgery until discharge from the hospital.

- **Excellent:** Abrupt pain relief and/or improvement in signs of bleeding within approximately 8 hours after the initial injection
- **Good:** Definite pain relief and/or improvement in signs of bleeding within approximately 8 hours after an injection, but possibly requiring more than one injection after 24 – 48 hours for complete resolution
- **Moderate:** Probable or slight beneficial effect within 8 hours after the initial injection **and** requires more than one injection
- **None:** No improvement, or condition worsens within approximately 8 hours after the initial injection

The following evaluations will determine the level of hemostasis achieved with rFIXFc treatment during surgery:

- Number of injections and dose per injection required to maintain hemostasis during the surgical period
- Estimated blood loss during surgery (intra-operative period)
- Number and type of blood component transfusions required during surgery

APPENDIX D. PHYSICIAN'S GLOBAL ASSESSMENT OF RESPONSE

Investigators will record assessments of each subject's response to his rFIXFc regimen using the following 4-point scale:

- **Excellent:** bleeding episodes responded to ≤ the usual number of injections or ≤ the usual dose of rFIXFc, or the rate of breakthrough bleeding during prophylaxis was ≤ that usually observed.
- **Effective:** most bleeding episodes responded to the same number of injections and dose, but some required more injections or higher doses, or there was a minor increase in the rate of breakthrough.
- **Partially Effective:** bleeding episodes most often required more injections and/or higher doses than expected, or adequate breakthrough bleeding prevention during prophylaxis required more frequent injections and/or higher doses.
- **Ineffective:** routine failure to control hemostasis or hemostatic control requires additional agents.

Investigators should consider the following, if available, when making the assessment:

- Frequency of rFIXFc injections
- Response to rFIXFc injection
- Information reported in the eDiary by the subject

APPENDIX E. PHYSICIAN ASSESSMENT OF RESPONSE TO TREATMENT DURING SURGERY

The Investigator/Surgeon who completed the minor or major surgical procedures will assess the subject's response to surgery with rFIXFc treatment using a 4-point clinical scale. This includes observations made during surgery. This assessment will be done within 24 hours after the surgery.

Excellent: intra-operative and post-operative blood loss similar to (or less than) the non-hemophilic patient.

- No extra doses of rFIXFc needed **AND**
- Blood component transfusions required are similar to person without hemophilia

Good: intra-operative and/or post-operative bleeding slightly increased over expectations for the non-hemophilic patient, but the difference is not clinically significant.

- Intra-operative blood loss no more than expected for a person without hemophilia **AND**
- No extra doses of rFIXFc needed **AND**
- Blood component transfusions required are similar to person without hemophilia

Fair: intra-operative and/or post-operative blood loss is increased over expectation for the person without hemophilia and additional treatment is needed.

- Intra-operative blood loss greater than expected for person without hemophilia **OR**
- Extra dose of rFIXFc needed **OR**
- Increased blood component transfusion requirement

Poor/none: significant intra-operative and/or post-operative bleeding that is substantially increased over expectations for the person without hemophilia, requires intervention, and is not explained by a surgical/medical issue other than hemophilia

- Intra-operative blood loss greater than for the person without hemophilia **OR**
- Unexpected hypotension or unexpected transfer to intensive care unit due to bleeding **OR**
- Substantially increased blood component transfusion requirement

APPENDIX F. PATIENT REPORTED OUTCOMES

The following quality of life questionnaires will be presented under separate cover:

- Haem-A-QoL
- Haemo-QoL
- Hemo-Sat-P Patient Satisfaction Scale for parents/guardians, Version 15
- CHO-KLAT
    - Children, Version 2.0 (for children previously enrolled in study 9HB02PED who are less than 18 years of age).
    - Proxy, Version 2.0p (for parents/guardians of children who were previously enrolled in study 9HB02PED and who are less than 18 years of age)
- EQ-5D Y
- EQ-5D 3L