Biogen Idec MA Inc.
14 Cambridge Center
Cambridge, MA 02142, USA

Biogen Idec Research Limited
Innovation House
70 Norden Road
Maidenhead Berkshire
SL6 4AY
United Kingdom

PROTOCOL NUMBER: 8HA01EXT

PHASE OF DEVELOPMENT: 3

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

EUDRA CT NO: 2011-003072-37

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SIGNATURE PAGE

Protocol 8HA01EXT, Version 3, was approved by:

[redacted]

[redacted]
Date

[redacted], Clinical Development
Biogen Idec MA Inc.

[redacted]

[redacted]
Date

[redacted], Clinical Development
Biogen Idec MA Inc.

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1. SPONSOR INFORMATION AND CONTACT INFORMATION

This study is sponsored by Biogen Idec MA Inc.

Biogen Idec MA Inc.
14 Cambridge Center
Cambridge, MA 02142
USA
Phone: +1 617-679-2000
Fax: +1 617-679-2617

Biogen Idec Research Ltd.
Innovation House
70 Norden Road
Maidenhead, Berkshire
SL6 4AY
United Kingdom
Phone: +44-1628 501000
Fax: +44-1628 501010

Biogen Idec Japan Ltd.
Atago Green Hills Mori
Tower 26F
5-1Atago 2-chome
Minato-ku
Tokyo 105-6226
Japan
Phone: +81 3 6402-7800
Fax: +81 3 6402-7850

Biogen Idec Canada
90 Burnahamthorpe Road West
Suite 1100
Mississauga, Ontario L5B 3C3
Canada
Phone: +1 905-804-1444
Fax: +1 905-897-3222

Biogen Idec Australia Pty Ltd
Suite 1, Level 5, 123 Epping Rd
North Ryde, NSW 2113
Australia
Phone**:** +61 2 8875 3900
Fax**:** +61 2 9889 1162

Primary contact for urgent medical issues:

[redacted], Medical Research:
Biogen Idec MA Inc.
[redacted]

Secondary contact for urgent medical issues:

[redacted] Medical Research
Biogen Idec MA Inc.
[redacted], MD
[redacted]

Other Contacts:

Clinical Research Organization:	Quintiles 4820 Emperor Boulevard Durham, NC 27703 USA
Pharmacovigilance/SAE Reporting	Quintiles Lifecycle Safety

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
BUN	Blood urea nitrogen
CHO-KLAT	Canadian Hemophilia Outcomes-Kids' Life Assessment Tool
C_{max}	Maximum activity
CRO	Contract research organization
DHA	Directions for Handling and Administration
eCRF	Electronic case report form
ED	Exposure day(s)
EDC	Electronic data capture
eDiary	Electronic patient diary
EOT	End of Treatment
FcRn	Neonatal Fc receptor
FVIII	Factor VIII
FVIII:C	Factor VIII coagulant activity
GCP	Good Clinical Practice
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
PHI	Protected health information
PK	Pharmacokinetics
PTP	Previously treated patient
QoL	Quality of life
rFVIIIFc	Recombinant human Factor VIII
SAE	Serious adverse event
SUSAR	Suspected unexpected serious adverse event
$t_{1/2}$	Half-life
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:	8HA01EXT
Protocol Title:	An Open-Label, Multicenter Evaluation of the Long-Term Safety and Efficacy of Recombinant Human Coagulation Factor VIII Fusion Protein (rFVIIIFc) in the Prevention and Treatment of Bleeding Episodes in Previously Treated Subjects With Hemophilia A.
Version Number:	3
Name of Study Treatment:	rFVIIIFc (BIIB031)
Study Indication:	Hemophilia A
Phase of Development:	3
Rationale for the Study:	To evaluate the long-term safety of rFVIIIFc for prevention and on-demand treatment of bleeding episodes in subjects with hemophilia A, and to allow subjects from the A-LONG pivotal study (997HA301), the pediatric study (8HA02PED), or any other rFVIIIFc study to continue treatment with rFVIIIFc.
Study Objectives and Endpoints:	**Objectives** Primary: The primary objective of the study is to evaluate the long-term safety of rFVIIIFc in subjects with hemophilia A. Secondary: The secondary objective of the study is to evaluate the efficacy of rFVIIIFc in the prevention and treatment of bleeding episodes in subjects with hemophilia A. **Endpoints** Primary: The occurrence of inhibitor development Secondary: • The annualized number of bleeding episodes (spontaneous and traumatic) 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 rFVIIIFc 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 assessment of response to the treatment of bleeding episodes using a 4-point scale

Major Surgery Endpoints:

- 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 post-operative period
- Number of blood product units transfused during surgery

Patient-Reported Outcomes Endpoints

Subjects will only take the Quality of Life (QoL) measurements that they completed during the parent study, which could include:

- Haem-A-QoL
- Haemo-QoL
- Hemo-Sat-Patient Satisfaction Scale for parents/guardians, Version 15
- Canadian Hemophilia Outcomes-Kids' Life Assessment Tool (CHO-KLAT)
    - Children, Version 2.0 (for children previously enrolled in study 8HA02PED who are less than 18 years of age).
    - Proxy, Version 2.0p (for parents/guardians of children previously enrolled in study 8HA02PED and who are less than 18 years of age)
- EQ-5D-Y
- EQ-5D-3L

Subjects will only take the health outcomes measurements related to hemophilia that they completed during the parent study, which could include:

- 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 subject or parent/caregiver
Study Design:	This is an open-label, multicenter, long-term study of intravenous (IV) administration of rFVIIIFc in previously treated patients with hemophilia A, who have completed the A-LONG study (997HA301), the pediatric study (8HA02PED), or any other trial with rFVIIIFc. Treatment will be administered as tailored prophylaxis (individualized), weekly (modified) prophylaxis, personalized prophylaxis, or on-demand (episodic) regimens. The regimens will hereafter be referred to as tailored prophylaxis, weekly prophylaxis, personalized prophylaxis, or on-demand.
Rationale for Dose and Schedule Selection:	Subjects will follow a tailored prophylaxis, weekly prophylaxis, personalized prophylaxis, or on-demand regimen. The choice of regimen will be based on the clinical profile of the subject and by the trough or peak (recovery) values, if needed, as observed in the preceding study. Subjects 12 years of age or older are allowed to change from prophylaxis to on-demand, or from on-demand to prophylaxis during the study. However, subjects less than 12 years of age will receive only a tailored or personalized prophylactic regimen. 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. The starting dose in study 8HA01EXT may be based on a subject's dose and dosing interval from the preceding rFVIIIFc study. In the completed Phase 3 study 997HA301 subjects initiated a dosing regimen of 25 IU/kg on Day 1 and 50 IU/kg on Day 4. The dose for each subject was subsequently adjusted between 25 IU/kg and 65 IU/kg and was given every 3 to 5 days based on the subjects' PK data and bleeding episodes. The maximum dose allowed was 65 IU/kg every 3 days. In the pediatric study, 8HA02PED, a dosing regimen with starting doses of 25 IU/kg on Day 1 and 50 IU/kg on Day 4 are being evaluated, with dose adjustments up to maximum prophylactic dose of 80 IU/kg and frequency of administration up to every 2 days if necessary to maintain adequate FVIII activity trough levels and prevent spontaneous bleeding events.
Treatment Regimen:	Details for each dosing regimen, 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 by the Investigator. **On-Demand Regimen** The individual dose of rFVIIIFc to treat bleeding episodes will be

based on the subject's clinical condition, type and severity of the bleeding event, and in some cases, FVIII peak (recovery) levels. Pharmacokinetic (PK) data and dosing levels from the preceding studies can also be used to guide dosing decisions. Subjects less than 12 years of age will receive a tailored or personalized prophylactic regimen and will not have the option to receive an on-demand regimen, but can receive an on-demand regimen once they reach the age of 12 years during the study.

Prophylaxis Dosing Regimens

- Option 1: Tailored Prophylaxis

The Investigator may consider the following options to target a FVIII trough of up to 5%, but is encouraged to use the lowest effective dose targeting a FVIII trough level between 1% and 3%. If bleeding episodes occur at FVIII 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%.

Dosing is approximately 25 IU/kg to 65 IU/kg every 3 to 5 days, or dosing 2 times per week at approximately 20 IU/kg to 65 IU/kg on Day 1 and 40 IU/kg to 65 IU/kg on Day 4. The dosing interval should be based on the subject's clinical profile observed in the preceding rFVIIIFc study, and/or his individual PK (if available), and FVIII trough and/or peak (recovery) values. For pediatric subjects <12 years of age, dose levels may be increased to a maximum prophylactic dose of 80 IU/kg and dose intervals decreased to every 2 days.

- Option 2: Weekly Prophylaxis

Dosing is approximately 65 IU/kg at weekly intervals. The dose should be based on the subject's clinical profile observed in the preceding rFVIIIFc study and/or his individual PK (if available), and FVIII trough and/or peak (recovery) values. Subjects less than 12 years of age will not have the option to receive a weekly prophylaxis regimen, but can receive a weekly prophylaxis regimen once they reach the age of 12 years during the study.

- 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 personalized prophylaxis dosing option will require consultation with the Medical Monitor. The Investigator may consider the following personalized dosing options:

- Addition of "prevention" doses prior to strenuous activity.
- Targeting a FVIII trough level of >3%, if the

bleeding history and/or activity level requires.

- Dosing less frequently.

The Investigator is not limited to the options above, and should consult the Medical Monitor for further consideration of a subject's dosing options.

Surgery:

If a subject requires surgery during this study, either emergent or elective, he may be treated with the dose and regimen of rFVIIIFc 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 Co-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 SAEs.

Rehabilitation period

If surgery-related dosing is to be continued during post-operative rehabilitation, the dose of rFVIIIFc will be adjusted to achieve a FVIII 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 rFVIIIFc 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, not required for minor surgery). Visit 4 (Last Post-Operative Visit) occurs when the subject returns to a regular rFVIIIFc regimen as determined by the Investigator, and is required only if the subject did not return to a regular rFVIIIFc

	regimen at Visit 3.
Study Location:	Global
Number of Planned Subjects:	Approximately 194 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 A. Detailed criteria are described in the body of the protocol.
Treatment Regimens:	Treatment regimens are defined as follows: • On-Demand: all subjects enrolled in the trial and treated using an on-demand regimen • Prophylaxis: all subjects enrolled in the trial and treated using a tailored prophylaxis, weekly prophylaxis, or personalized prophylaxis regimen There will also be a surgery subgroup, which is defined as a subset of subjects from the prophylaxis and on-demand regimens who have major surgery during the course of the trial.
Duration of Treatment and Follow-up:	Subjects first dosed with rFVIIIFc when <12 years of age will be followed to at least 100 EDs, even if rFVIIIFc becomes commercially available. All subjects will have the opportunity to continue in this study for up to 4 years or until rFVIIIFc is commercially available in the applicable participating country.
Definition of Dose-Limiting Toxicity:	No dose-limiting toxicity for rFVIIIFc has been identified.
Statistical Methods:	In general, the data for subjects who enroll from the parent studies will have their data integrated with their data from 8HA01EXT. A parent study is defined as a study where subjects may be enrolled into 8HA01EXT 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. 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 1 dose of rFVIIIFc will be included in the Full Analysis Set (FAS). Efficacy analyses will be based on the FAS. For subjects who have surgeries during the study, their efficacy data during the surgical period (including rehabilitation period) will be analyzed separately. The efficacy and surgical/rehabilitation periods will be defined in the statistical analysis plan for the purpose of determining the study periods during which data will be used for

	select efficacy analyses. Data on bleeding and rFVIIIFc consumption will be based on the efficacy period; surgical evaluations will be based on the surgical/rehabilitation period. Bleeding episodes will be annualized for each subject first, then summarized and tabulated by treatment arm, treatment regimen, or age cohort, as appropriate, in the parent studies. These analyses will also be performed for each type of bleed (spontaneous and traumatic). The number of spontaneous joint bleeding episodes and the consumption of rFVIIIFc will be annualized in a similar fashion and tabulated. Analysis of surgery endpoints will be performed for subjects who had surgeries during the study, either emergently or electively. Summary statistics of surgery endpoints will be provided for 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 change from baseline as appropriate. Summary statistics of health outcome endpoints will be tabulated at each collection timepoint. **Safety** The Safety Population will include all subjects with at least 1 dose of rFVIIIFc. For the analysis of safety, data in 8HA01EXT will be integrated with the parent studies, 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. Findings in clinical lab values will be summarized by descriptive statistics. The proportion of subjects with inhibitors during rFVIIIFc administration will be provided with the exact (Clopper-Pearson) 2-sided, 95% confidence interval.
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.
Sample Size Determination:	This is an extension study. Sample size is based on sample sizes of Studies 997HA301 (N=144) and 8HA02PED (N=50), and may be increased based upon subject participation in other rFVIIIFc 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 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 rFVIIIFc 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 rFVIIIFc. 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 8HA01EXT

Table 1: Screening and Treatment Period

Tests and Assessments[2]	Visit 1[1]	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 and Vital Signs [4]	X		X		X		X	X
Height	X		X		X		X	X
Weight	X	X	X	X	X	X	X	X
rFVIIIFc Dosing/Dispensation/Accountability[5]	X	X	X	X	X	X	X	X
Nijmegen-modified Bethesda Assay (inhibitor assay)[6]	X	X	X	X	X	X	X	X
Anti-rFVIIIFc antibody[6]	X	X	X	X	X	X	X	X
Hematology [6,7]	X	X	X	X	X	X	X	X
Blood Chemistry [6, 8]	X	X	X	X	X	X	X	X
FVIII Activity [6, 9]	X	X	X	X	X	X	X	X
DNA-Based Testing[10]	X							
QoL Questionnaires[11]	X	X	X	X	X	X	X	X
Health Outcomes[12]	X	X	X	X	X	X	X	X
Subject eDiary Review	X	X	X	X	X	X	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	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

Table 1: Screening and Treatment Period (Continued)

Tests and Assessments[2]	Unscheduled Visit[13]	Final Study Visit/ Early Termination Visit	Follow-Up[15] 7 (+7) days after last dose
Physical Examination and Vital Signs [4]		X	
Height		X	
Weight		X	
rFVIIIFc Dosing/Dispensation/Accountability[5]	X	X	
Nijmegen-modified Bethesda Assay (inhibitor assay)[6]		X	
Anti-rFVIIIFc antibody[6]		X	
Hematology [6, 7]		X	
Blood Chemistry [6, 8]		X	
FVIII Activity [6, 9]		X	
QoL Questionnaires[11]		X	
Health Outcomes[12]		X	
Subject eDiary Review	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

Table footnotes are presented on page 23.

Footnotes for Screening and Treatment Period

1. End of Treatment (EOT) visit for the preceding 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. 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 and/or designee. Data on medical history, demographics, screening tests, ongoing adverse events (AEs) and concomitant therapy, and EOT tests and assessments will be transferred from the preceding rFVIIIFc studies. Thus, 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 EOT Visit of the previous study should have all laboratory assessments performed and reviewed by the Investigator at Visit 1, prior to dosing with rFVIIIFc, to assess safety and inclusion/exclusion parameters. The time required for Visit 1 may span a sufficient interval to allow for laboratory results to be reviewed and confirmed as suitable by the Investigator, and may require more than 1 clinic visit prior to dosing with rFVIIIFc.
2. For future subjects that enroll into ASPIRE, assessments will be only those conducted in the parent study.
3. Medical and surgical history includes any significant medical condition and/or any significant surgical histories that have occurred since the subject enrolled in the parent study.
4. Physical examination and vital signs. Physical examination to include: skin, head, eyes, ears, nose, throat (HEENT); lymph; neck; chest/lungs; heart; vascular; abdomen; musculoskeletal; neurological; extremities; and joints. Vital signs to include: temperature, blood pressure, pulse rate, and respiratory rate. Following Visit 7, physical examination and vital signs continue to be performed only annually.
5. Subjects will receive supplies of rFVIIIFc 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 12 for information on planning and process for dispensation, and on supplies accountability.
6. To be performed at the central laboratory. FVIII activity is determined by one-stage aPTT clotting assay and two-stage chromogenic assay performed at the central laboratory. For FVIII inhibitor and rFVIIIFc antibody testing, a wash out of at least 48 hours is recommended. For subjects who have fewer than 50 exposure days (EDs) with rFVIIIFc 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 100 to 125 EDs, as applicable. If the timing does not coincide with a scheduled visit, an unscheduled visit may be conducted. A portion of the blood sample collected will be stored for future anti-rFVIIIFc antibody testing. Samples will be archived for testing (if required) for immunology or further coagulation assays, or for clarification of any clinical or laboratory AE. Inhibitor and rFVIIIFc antibody testing should also be done when deemed clinically relevant.
7. Hematology includes: white blood cell count (WBC), differential, platelet count, hemoglobin, hematocrit.
8. 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.
9. Tailored prophylaxis, weekly prophylaxis, and personalized prophylaxis regimens: FVIII activity to be measured at trough immediately prior to the injection, and at peak (recovery) 30 (±3) minutes from the start of injection. On-demand regimen: FVIII activity to be measured at the discretion of the Investigator.
10. The sample for DNA-based testing is optional and may be collected at any time during the study, not exclusively at Visit 1.

11. Patient-reported outcomes should be completed only if they were conducted during the parent study: Questionnaires to be completed every 6 months at scheduled clinic visits. Questionnaires will be provided under separate cover.
12. Changes in patient-reported health outcomes conducted during the parent study to be queried in the subject's electronic patient diary (eDiary) on an ongoing basis, and details to be recorded in the electronic case report form (eCRF).
13. Unscheduled visits may be necessary during the study, as determined by the Investigator, for reasons that may include repeating safety assessments, repeating blood sampling if required, or changing dose/regimen. For subjects from the pediatric study (8HA02PED) who undergo major 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 (see Section 5.3.3 for list of assessments). For subjects who have fewer than 50 EDs with rFVIIIFc 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 100 to 125 EDs, as applicable. If the timing does not coincide with a scheduled visit, an unscheduled visit may be conducted.
14. Subjects entering the extension study from 997HA301 should continue to use the Modified Hemophilia Joint Health Score. Subjects entering the extension study from 8HA02PED should continue to use the HJHS Version 2.1. HJHS and modified HJHS should only be completed if they were conducted during the parent study. Following Visit 7, the HJHS assessment continues to be performed annually. The HJHS assessment is not required at Final Study Visit if it was performed within the last 9 months.
15. A follow-up telephone visit is required 7 (+7) days after the last dose of rFVIIIFc to monitor AEs, SAEs, and concomitant medications and therapies. This 7 day follow-up visit is not required if a subject ends his participation in the extension study to enroll into another rFVIIIFc study, however, a final visit/early termination visit is required.

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[8]	Visit 4 Last Post-Operative Visit[8]
Physical Examination	X	X		X
Weight	X	X	X	X
Vital Signs (temperature, blood pressure, pulse rate, respiratory rate)		X[1]		
Hematology[3]	X	X	X	X
Blood Chemistry[3]	X	X	X	X
Subject's Assessment of Response[4]	<<<<<<<< ongoing as applicable >>>>>>			
Investigator/Surgeon Assessment of Hemostatic Response[5]		X		
FVIII Activity[6]	X	X	X	X
Nijmegen-modified Bethesda Assay (inhibitor testing)[7]	X	X	X	X
Anti-rFVIIIFc Antibody Assay[7]	X	X	X	X
rFVIIIFc Administration	X	X	X	X
AE/SAE Monitoring and Recording	X	X	X	X
Concomitant Therapy/Procedures Recording	X	X	X	X

Table footnotes are presented on page 25.

Footnotes for Surgery Visits

1. All tests and assessments should be collected for major surgery and minor surgery, where available. Subjects may be allowed to have a PK evaluation performed by the central laboratory prior to surgery if needed in the opinion of the Investigator.
2. To be assessed prior to surgery.
3. 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.
4. Subjects who require post-operative rFVIIIFc treatment for a bleeding episode at home will record their assessment of response to treatment in the eDiary; this assessment is to be made approximately 8 to 12 hours from the time the rFVIIIFc injection was given to treat the bleeding episode and prior to any additional doses of rFVIIIFc given for the same bleeding episode.
5. 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 within 24 hours after surgery. See Appendix C and Appendix E.
6. FVIII activity levels should be measured prior to the pre-operative (loading) dose of rFVIIIFc, and at 30 ± 5 minutes post-dosing. A repeat sample will be taken approximately 6 to 9 hours after this dose, but may alternatively follow the local standard of care for determination of subsequent rFVIIIFc dosing. During the subject's hospitalization, FVIII activity will be measured daily at the local laboratory, and a plasma aliquot will be prepared for each blood sample drawn for subsequent analysis at the central laboratory.
7. Inhibitor and anti-rFVIIIFc antibody testing 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 minor surgery, testing is not performed at the last 2 timepoints). For FVIII inhibitor and antibody testing, a wash out of at least 48 hours is recommended.
8. 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 rFVIIIFc regimen as determined by the Investigator, and is not required if the return to a regular rFVIIIFc regimen occurs at Visit 3.

5. INTRODUCTION

8HA01EXT is an extension study designed to assess the long-term safety and efficacy of recombinant factor VIII fusion protein (rFVIIIFc) in previously treated subjects with hemophilia A. Male subjects of all ages who have completed a preceding study of rFVIIIFc (997HA301, 8HA02PED, or any other rFVIIIFc study) may be eligible for enrollment in this study.

The Note for Guidance on the Clinical Investigation of Recombinant Factor VIII and Human Plasma-derived FVIII Products [CPMP, 2009] was followed in the development of this protocol.

5.1. Profile of Previous Experience

Hemophilia A is an X-chromosome-linked bleeding disorder caused by mutations and/or deletions in the F8 gene resulting in a deficiency of FVIII activity [Mannucci, 2001; Bolton-Maggs and Pasi, 2003]. The coagulation disorder occurs predominantly in males and affects approximately 1 in 10,000 males. The severity of disease is characterized by the endogenous level of FVIII measured in the plasma. Severe hemophilia A is defined as a coagulation activity of FVIII in plasma (FVIII:C) level of <1% (<1 IU/dL). Individuals with severe hemophilia A experience frequent bleeding and recurrent spontaneous bleeding into the soft tissue and joints, leading to joint damage and severe disability. Repeated bleeding into muscles and joints, which often begins in early childhood, results in hemophilic arthropathy and irreversible joint damage. Damage can lead to limited mobility of joints, muscle atrophy, and chronic pain [Rodriguez-Merchan, 2003].

FVIII and factor IX work in concert to activate factor X, a central step in the clotting cascade. The coagulation cascade has 2 pathways, the Contact Activation Pathway (Intrinsic Pathway) and the Tissue Factor Pathway (Extrinsic Pathway). The plasma factors are activated in a cascade one after the other until the soluble plasma protein fibrinogen is transformed into a fibrinous clot.

5.1.1. Therapies for Hemophilia A

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

The use of FVIII-containing plasma-derived coagulation products for people with hemophilia A, available for almost 40 years, has led to vast improvements in quality of life and has increased

life expectancy. Manufacturing methods for plasma-derived products are now considered to be highly effective in reducing the risk of transmission of enveloped viruses such as HIV and hepatitis B and C. However, these methods may not be effective in reducing the risk of nonenveloped viruses, such as hepatitis A and parvovirus B19. Recombinant coagulation products developed more recently with no animal or human plasma-derived proteins have a safety advantage with a minimal risk of disease transmission [Mannucci, 2001].

Priorities for improving hemophilia A therapy include the development of more convenient dosing options and development of modified FVIII agents with longer half-life ($t_{1/2}$) 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 patients' quality of life and functional independence [Colvin, 2008].

5.1.2. rFVIIIFc

rFVIIIFc is a novel recombinant Fc fusion protein comprised of a single molecule of B-domain-deleted FVIII attached to the Fc domain of human immunoglobulin G1 (IgG1). This type of construct has been termed a monomeric Fc fusion protein [Dumont 2006]. The Fc enables binding to the neonatal Fc receptor (FcRn), which is responsible for protecting IgG from degradation and confers IgG the 3-week $t_{1/2}$ observed in humans [Ghetie and Ward 2000; Roopenian 2007]. The FcRn is present in humans throughout life and protects IgG from catabolism [Junghans 1996]. rFVIIIFc was designed to offer a longer circulating $t_{1/2}$ than currently available FVIII products, aiming to provide hemophilia A patients with prolonged protection and prophylaxis from bleeding with less frequent dosing.

5.1.3. Summary of Clinical Experience With rFVIIIFc

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

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

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

When compared with Advate at both dose levels, rFVIIIFc was well-tolerated. No clinically significant changes in safety parameters occurred and most adverse events (AEs) were mild and resolved without sequelae by the end of the study. No subject developed antibodies or inhibitors during the study period. Compared with Advate, rFVIIIFc demonstrated significantly improved

activity, as indicated by longer $t_{1/2}$, increased systemic exposure, and a reduction in clearance, with comparable maximum plasma activity (C_{max}) and recovery. Improved FVIII activity resulted in an increased time to 1% above baseline, approximately 50% to 74% longer at doses of 25 IU/kg and 65 IU/kg, respectively (one-stage aPTT clotting assay); and 51% to 79% longer at 25 IU/kg and 65 IU/kg, respectively (chromogenic assay).

In addition, a Phase 3 study in previously treated subjects age 12 years or older with severe hemophilia A has recently been completed (Study 997HA301). A total of 164 subjects (including 13 subjects aged 12 to 17 years) in the Phase 3 study received at least 1 dose of rFVIIIFc. This included 146 subjects treated for at least 26 weeks and 23 subjects treated for at least 39 weeks, for a total of 102.05 person-years on study.

Compared with Advate, rFVIIIFc demonstrated improved PK activity, as indicated by a 53% longer $t_{1/2}$, a 56% increase in systemic exposure, and a 36% reduction in CL, with comparable C_{max} and recovery (one-stage aPTT clotting assay).

rFVIIIFc was well tolerated in the Phase 3 study. No subject developed an inhibitor to rFVIIIFc. Common AEs observed were consistent with those expected in patients with hemophilia A. Adverse drug reactions were mild and manageable, and the majority were not treatment limiting. One nonserious event of rash required discontinuation of treatment and resolved. There was no Grade 2 or greater allergic reactions or serious vascular thrombotic events. No treatment-related serious adverse events (SAEs) were observed.

Study 8HA02PED (referred to as the pediatric study) is an open-label, multicenter study evaluating the safety, PK, and efficacy of rFVIIIFc in previously treated pediatric patients with severe hemophilia A, who are <12 years of age, and have at least 50 EDs to FVIII products prior to enrollment. Approximately 50 male subjects (25 subjects <6 years of age and 25 subjects 6 to <12 years of age) are planned to complete at least 26 weeks of prophylactic treatment to attain at least 50 EDs. At least 24 of these subjects (12 subjects <6 years of age and 12 subjects 6 to <12 years of age) will undergo an evaluation of the PK profile of pre-study FVIII and rFVIIIFc. 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 rFVIIIFc, please refer to the rFVIIIFc Investigator's Brochure.

5.2. Study Rationale

The results of the Phase 1/2a study, the nonclinical data [Dumont, 2009], and the Phase 3 study support further investigation of repeat administration of rFVIIIFc in the prevention and treatment of bleeding episodes in hemophilia A subjects. This extension study will evaluate the long-term safety of rFVIIIFc in subjects with hemophilia A and will allow subjects from the A-LONG (997HA301) pivotal study, the pediatric study (8HA02PED), and other studies to continue treatment with rFVIIIFc.

5.3. Rationale for Dose and Schedule Selection

Subjects 12 years of age or older will follow either a tailored prophylaxis (individualized), weekly (modified) prophylaxis, personalized prophylaxis, or on-demand (episodic) regimen based on the clinical profile of the subject and by the trough and/or peak (recovery) values, if needed, as observed in the preceding study. Subjects are allowed to change treatment regimens (for example, from prophylaxis to on-demand, or from on-demand to prophylaxis) during the study. Subjects less than 12 years of age will receive 1 of 2 prophylactic regimens, tailored or personalized, and will not have the option to change to a weekly prophylactic or on-demand regimen, unless they reach the age of 12 years during the study, at which time they can be use any of the 4 treatment regimens. 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. All regimen changes must occur at a scheduled or unscheduled clinic visit following assessment by the Investigator, and must be documented at that visit. 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 8HA01EXT may be based on the subject's results from the preceding rFVIIIFc study. In the completed Phase 3 study, 997HA301, doses between 20 IU/kg and 65 IU/kg were evaluated and shown to successfully maintain a trough level >1% and/or control bleeding. In the pediatric study, 8HA02PED, a regimen consisting of starting doses of 25 IU/kg on Day 1 and 50 IU/kg on Day 4 of rFVIIIFc is used initially. This dosing regimen may be adjusted as indicated by enrollment PK, subsequent FVIII activity trough levels, or bleeding patterns: the dose may be adjusted up to a maximum prophylactic dose of 80 IU/kg and the frequency of administration up to every 2 days, if necessary to maintain adequate FVIII activity trough levels and prevent spontaneous bleeding events.

5.3.1. On-Demand Regimen

The individual dose of rFVIIIFc to treat bleeding episodes will be based on the subject's clinical condition, type and severity of the bleeding event, and if indicated, FVIII levels. A subject's PK profile and dosing levels from the predecessor studies may also be used to guide dosing decisions. Subjects <12 years of age entering from another rFVIIIFc study will not be offered this option, but can receive an on-demand regimen once 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

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.

5.3.2.1. Option 1: Tailored Prophylaxis

The Investigator may consider the following options for tailored prophylaxis to target a FVIII trough of up to 5%, but is encouraged to use the lowest effective dose targeting a FVIII trough

level between 1% and 3%. If bleeding episodes occur at FVIII 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%.

Dosing is approximately 25 IU/kg to 65 IU/kg every 3 to 5 days, or dosing 2 times per week at approximately 20 IU/kg to 65 IU/kg on Day 1 and 40 IU/kg to 65 IU/kg on Day 4. The dose and interval should be based on the subject's clinical profile observed in the preceding rFVIIIFc study, and/or his individual PK (if available), and FVIII trough and/or peak (recovery) values. In pediatric subjects, doses may be adjusted up to a maximum prophylactic dose of 80 IU/kg and the interval decreased to every 2 days, if necessary to maintain adequate FVIII activity trough levels and prevent spontaneous bleeding events.

5.3.2.2. Option 2: Weekly Prophylaxis

Dosing is approximately 65 IU/kg at weekly intervals. The dose should be based on the subject's clinical profile observed in the preceding rFVIIIFc study, and/or his individual PK (if available), and FVIII trough and/or peak (recovery) values. Subjects <12 years of age entering from another rFVIIIFc study will not be offered this option, but can receive a weekly prophylaxis regimen once they reach the age of 12 years during the study.

5.3.2.3. 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 FVIII trough level of >3%, if the bleeding history and/or activity level requires.
- Dosing less frequently.

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.

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 rFVIIIFc 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 Co-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 when a subject requires major surgery.

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

Subjects will return to a regular rFVIIIFc 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, not required for minor surgery). Visit 4 (Last Post-Operative Visit, not required for minor surgery) occurs when the subject returns to a regular rFVIIIFc regimen as determined by the Investigator, and is required only if the subject did not return to a regular rFVIIIFc regimen at Visit 3.

The surgical period will begin with the subject's first dose of rFVIIIFc 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 rFVIIIFc 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 the pediatric study (8HA02PED) who undergo major surgery and enter the extension study before completing their Last Post-Operative Visit from the prior rFVIIIFc 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 rFVIIIFc regimen (as outlined in Sections 5.3.1 and 5.3.2). The following assessments must be performed at that time:

- Physical examination
- Weight
- Hematology
- Subject's assessment of response
- FVIII activity (to be measured at trough immediately prior to the injection and at peak [recovery] 30 [±3] minutes from the start of injection)
- Subject eDiary review
- Nijmegen-modified Bethesda assay (inhibitor assay)
- rFVIIIFc 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 rFVIIIFc.

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 rFVIIIFc in subjects with hemophilia A.

6.1.2. Secondary Objectives

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

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 (spontaneous and traumatic) 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 rFVIIIFc 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 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 post-operative period
- Number of blood product units transfused during surgery

6.2.4. Patient-Reported Outcome Endpoints

The following patient-reported outcomes will be assessed. Subjects will only take the questionnaires that they completed during the parent study. If a subject goes outside of the age range for a questionnaire, they should no longer complete the questionnaire. The Investigator will administer the age-appropriate questionnaire at the appropriate visits.

Quality of Life (QoL) questionnaires:

- Haem-A-QoL
- Haemo-QoL
- Hemo-Sat-Patient Satisfaction Scale for parents/guardians, Version 15
- Canadian Hemophilia Outcomes-Kids' Life Assessment Tool (CHO-KLAT)
    - Children, Version 2.0 (for children previously enrolled in study 8HA02PED who are less than 18 years of age).
    - Proxy, Version 2.0p (for parents/guardians of children previously enrolled in study 8HA02PED and who are less than 18 years of age)
- EQ-5D Y
- EQ-5D-3L

Health outcomes related to hemophilia will include:

- 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, day care, or preschool
- Number of days off work for the parent or caregiver

7. STUDY DESIGN

7.1. Study Overview

This is an open-label, multi-center, long-term study of IV administration of rFVIIIFc in previously treated patients (PTPs) with hemophilia A who have completed the A-LONG study (997HA301), the pediatric study (8HA02PED), or any other study with rFVIIIFc. This is a global study and will be offered to those countries participating in these studies.

Based on estimated sample sizes from these studies, approximately 194 subjects from the ongoing A-LONG study and the pediatric study may be eligible to enroll in this extension study. The End of Treatment (EOT) Visit of the previous study may serve as the initial visit of 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 prior rFVIIIFc 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 (see Section 5.3.3 for list of assessments). For subjects who have fewer than 50 exposure days (EDs) with rFVIIIFc following completion of Visit 1, a visit may be conducted to perform inhibitor testing at the time subjects reach 10-15 EDs, 50-75 EDs, and 100-125 EDs, as applicable. If the timing 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 is required 1-2 weeks after surgery (Visit 3, not required for minor surgery). Visit 4 is required only if subjects who had major surgery did not return to a regular rFVIIIFc regimen as determined by the Investigator at Visit 3. All major surgeries will be reported as SAEs. Scheduled visits will include safety and efficacy assessments, and FVIII activity measurements to assess trough and peak (recovery) (Section 4). In addition, the site will continue to contact study subjects and/or caregivers by telephone on a bimonthly basis to review AEs, treatment compliance, and use of concomitant medications and therapies.

Treatment will be administered as tailored prophylaxis, weekly prophylaxis, personalized prophylaxis, or as an on-demand regimen. 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 1 of 2 prophylactic regimens, tailored or personalized, and will not have the option to change to a weekly prophylactic or on-demand regimen, unless they reach the age of 12 years during the study, at which time they can use any of the 4 treatment regimens.

To ensure accuracy of FVIII trough/peak (recovery) and inhibitor testing, subjects following a prophylaxis regimen should schedule clinic visits 48 hours after the previous dose of rFVIIIFc, whenever possible.

Subjects first dosed with rFVIIIFc when <12 years of age will be followed to at least 100 EDs, even if rFVIIIFc becomes commercially available.

All subjects will have the opportunity to continue in this study for up to 4 years or until rFVIIIFc 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 rFVIIIFc up to 65 IU/kg. Also, no dose-limiting toxicities were observed in the preclinical animal studies where repeat doses of up to 1000 IU/kg were evaluated.

Doses higher than 65 IU/kg may be used in this study, such as in surgery, to achieve the required FVIII levels to prevent bleeding. However, the maximum dose during surgery will not exceed the predicted accumulated C_{max} of approximately 200% of normal (normal ranges are 50-150% FVIII activity). In pediatric subjects, dose adjustments up to a maximum prophylactic dose of 80 IU/kg and frequency of administration up to every 2 days can be used if necessary to maintain adequate FVIII activity trough levels and prevent spontaneous bleeding events.

An overdose of rFVIIIFc is defined as any single prophylactic dose >100 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, the expected plasma FVIII activity levels are not attained, or if bleeding is not controlled as expected following dosing), inhibitor testing will be performed by the central laboratory. The definition of a positive result for 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 of the sample must be sent in parallel to the central laboratory.

For FVIII inhibitor testing, a wash out of at least 48 hours is recommended.

For subjects who have fewer than 50 exposure days (EDs) with rFVIIIFc following completion of Visit 1, a visit may be conducted to perform inhibitor testing at the time subjects reach 10-15 EDs, 50-75 EDs, and 100-125 EDs, as applicable. If the timing does not coincide with a scheduled visit, an unscheduled visit may be conducted.

7.1.3. Anti-rFVIIIFc Antibody Testing

In order to characterize non-neutralizing antibodies that may react with rFVIIIFc, an exploratory assay that differentiates between antibodies with specificities for rFVIIIFc, full-length FVIII (Advate®), or Fc will be used to test for the presence of anti-drug antibody in study subjects.

The electrochemiluminescent assay (ECLA) used for this test is approximately 10-to 20-fold more sensitive than the Nijmegen-modified Bethesda assay. A blood sample will be stored for future testing of anti-rFVIIIFc antibody at the same time points that samples are drawn for inhibitor testing, or for any clinical event deemed relevant to anti-rFVIIIFc testing (see Table 1 and Table 2).

7.1.4. Bleeding Episodes

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

In this study, when a subject reports a bleed or hemorrhage, and is treated with study drug, it will be classified as spontaneous or traumatic by the subject. The subject's eDiary will serve as the source document for bleeding episodes while on 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. Both spontaneous bleeding episodes (the occurrence of hemorrhage where neither the subject nor a caregiver can identify a reason) and traumatic bleeding episodes (hemorrhage occurring secondary to an event such as trauma or strenuous activity) will be collected. 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 in the absence of any obvious injury, the bleed would still 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 incidence of bleeding in this study will be obtained from eDiaries and any medical records 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 monitors will ensure that there is consistency between the subject's eDiary record and eCRFs. During the clinical visits and 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 dose 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, or related to increased physical activity).
- The date the bleeding event 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 rFVIIIFc to treat the bleeding episode will be based on the subject's clinical condition, known PK information from the previous study or FVIII trough/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 with a single dose of rFVIIIFc. Most bleeding episodes should resolve with a single dose of rFVIIIFc. 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 rFVIIIFc,** the subject should return to his previous dosing regimen and will be treated with his next dose of rFVIIIFc as previously scheduled, even if this results in consecutive daily doses.
- **If the bleeding episode does not stop within 24 hours with the single IV dose of rFVIIIFc,** the subject or the subject's caregiver should consult with the Investigator for an optimal rFVIIIFc dose and dosing interval, and should administer a second dose (first follow-up dose) no less than 24 hours after the initial dose. Administration of the second dose of rFVIIIFc as follow-up treatment will be determined by the Investigator based on the subject's clinical condition. Please refer to Appendix A for rFVIIIFc 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 rFVIIIFc 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 rFVIIIFc,** the subject or the subject's caregiver should contact the Investigator for advice. Following consultation with the Investigator, a third dose of rFVIIIFc will be administered 24 hours after the administration of the second dose of rFVIIIFc. The third dose (second follow-up dose) may be at the same dose as the second dose or a dose determined by the Investigator based on the subject's clinical condition. Please refer to Appendix A for rFVIIIFc 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 rFVIIIFc 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 rFVIIIFc, 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 a subject experiences ≥2 moderate or major spontaneous bleeding episodes over a rolling 8-week period. The Investigator can adjust the rFVIIIFc 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 description of regimen changes.

7.2. Overall Study Duration and Follow-Up

The study period will consist of Screening and Treatment.

Subjects first dosed with rFVIIIFc when <12 years of age will be followed to at least 100 EDs, even if rFVIIIFc becomes commercially available.

All subjects will have the opportunity to participate in this study for up to 4 years or until rFVIIIFc 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 preceding study may act as Visit 1 for this study, however, if there is a gap of >37 days following the EOT Visit of the preceding study, all laboratory assessments for Visit 1 must be performed and eligibility confirmed prior to dosing with rFVIIIFc.

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

7.2.2. Treatment

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

7.2.3. Follow-Up

A final study visit will be conducted approximately 147 (+7) days after the last dose of rFVIIIFc. This 7 day follow-up visit is not required if a subject ends his participation in the extension study to enroll into another rFVIIIFc 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 high titer (i.e. ≥5.00 BU/mL) inhibitor, as defined in Section 7.1.2. This number can be adjusted based on sample size when more subjects might be included into this trial from other rFVIIIFc 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 rFVIIIFc. 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 last subject, 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:

1. Ability to understand the purpose and risks of the study and 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.
2. Subjects who have completed the studies 997HA301, 8HA02PED, or other studies with rFVIIIFc.

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 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 rFVIIIFc 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 rFVIIIFc 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 rFVIIIFc 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 rFVIIIFc are provided in the Drug Handling and Administration (DHA) Manual.

rFVIIIFc will be administered over several minutes by slow 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 12 years of age or older will follow either a tailored prophylaxis, weekly prophylaxis, personalized prophylaxis, or an on-demand regimen based on the subject's clinical profile and by PK profiles and dosing levels from the prior rFVIIIFc study. Subjects will be allowed to change from a prophylaxis regimen to on-demand and from on-demand to prophylaxis during this 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.

Subjects less than 12 years of age will receive 1 of 2 prophylactic regimens, tailored or personalized, and will not have the option to change to a weekly prophylactic or on-demand regimen, unless they reach the age of 12 years during the study, at which time they can be use any of the 4 treatment regimens.

10.1.1. Prophylaxis Regimens

The tailored prophylaxis regimen may comprise weekly doses of 25 IU/kg to 65 IU/kg rFVIIIFc every 3 to 5 days or dosing 2 times per week at approximately 20 IU/kg to 65 IU/kg rFVIIIFc on Day 1 and 40 IU/kg to 65 IU/kg rFVIIIFc on Day 4. In pediatric subjects, dose adjustments up to a maximum prophylactic dose of 80 IU/kg and frequency of administration up to every 2 days can be used if necessary to maintain adequate FVIII activity trough levels and prevent spontaneous bleeding events.

The weekly prophylaxis dosing regimen comprises once weekly dosing of approximately 65 IU/kg rFVIIIFc.

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 personalized prophylaxis dosing option will require consultation with the Sponsor Medical Monitor.

Please refer to Section 5.3.2 for descriptions of the tailored prophylaxis, weekly prophylaxis, and personalized prophylaxis dosing options.

10.1.2. On-Demand Regimen

The individual dose of rFVIIIFc 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 another rFVIIIFc study will not have the option of an on-demand regimen, but can receive an on-demand regimen once 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 rFVIIIFc 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 consult by the Investigator or Co-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 rFVIIIFc 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 Principal Investigator.
2. The Investigator and/or appropriate qualified/licensed delegate is available to
    a. Administer all rFVIIIFc 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.

Inhibitor 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, and at the last post-operative visit (for minor surgery, testing is not performed at the last 2 timepoints). On the day of surgery, subjects will be given a pre-operative loading dose of rFVIIIFc as a bolus, and, in the case of emergency

surgery, as soon as possible prior to the procedure. Pre-dose FVIII activity levels will be sampled followed by FVIII peak (recovery) samples 30 ± 5 minutes post-dosing.

A repeat sample will be taken approximately 6 to 9 hours after this dose, but may alternatively follow the local standard of care for determination of subsequent rFVIIIFc dosing. During the subject's hospitalization, FVIII 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 65 IU/kg may be used in the context of surgery to achieve the required FVIII 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 200% of normal (normal ranges are 50% to 150% FVIII 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 caused directly by surgery should not be reported, although undesired or unexpected bleeding during or after surgery should be recorded on the eCRF.

10.2. Treatment Precautions

Precautions should be taken with any FVIII product.

The subject will be provided with specific instructions by the Investigator 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 for details on prophylaxis regimens.

10.3.2. On-Demand Regimen

rFVIIIFc doses to treat bleeding episodes will be based on the subject's clinical condition, type and severity of the bleeding episode, and in some cases, FVIII peak (recovery) levels. A subject's PK profile and dosing levels from the previous rFVIIIFc studies 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 7 (+7) days after the last dose of rFVIIIFc in this extension study. Concomitant medications, procedures, or therapies must be recorded on the subject's eCRF, according to the instructions for eCRF completion. 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 including only low dose acetylsalicylic acid (≤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 (other non-steroidal anti-inflammatory drugs are permitted).

  The use of low-dose acetylsalicylic acid may be allowed, with approval of the Sponsor Medical Monitor, for subjects who have (or develop) a medical condition requiring this treatment and who remain under the medical supervision of the prescribing physician during the course of the study.
- Current systemic treatment with chemotherapy and/or other immunosuppressant drugs (unless advised otherwise after consult with the Medical Monitor)
- Any other FVIII 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, and 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. AEs related to administration of these therapies or procedures must be documented on the appropriate eCRF.

10.6. Continuation of Treatment

If rFVIIIFc is proven to be beneficial, all regulatory requirements regarding post-study access will be met.

Subjects first dosed with rFVIIIFc when <12 years of age will be followed to at least 100 EDs, even if rFVIIIFc becomes commercially available.

All subjects will have the opportunity to continue in this study for up to 4 years or until rFVIIIFc 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 rFVIIIFc for any of the following reasons:

- A Grade 2 or greater allergic drug reaction in association with administration of rFVIIIFc, 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 rFVIIIFc; no parenteral therapy needed
    - Grade 3 Bronchospasm related to rFVIIIFc; parenteral therapy required
    - Grade 4 Anaphylaxis related to rFVIIIFc
- A high-titer inhibitor (≥5.00 BU/mL), as defined in Section 7.1.2.
- Use of FVIII products other than rFVIIIFc, unless it occurs in 1 life-threatening emergency and/or as a result of 1 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 rFVIIIFc, 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 1 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 DHA for full details regarding rFVIIIFc.

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).**

In between visits, the subject or the subject's caregiver must return to the investigational site for dispensation of rFVIIIFc and administration supplies before the earliest expiration date of drug in the subject's inventory. This is to maintain adequate drug supplies for his treatment, including an adequate supply to treat breakthrough bleeding or due to delays in scheduling clinic visits.

12.1. rFVIIIFc (BIIB031)

rFVIIIFc lyophilized powder is provided in a clear glass vial containing 250, 500, 1000, 2000, or 3000 IU of rFVIIIFc (nominal strengths). Not all strengths may be available at the start of the study. In addition to the rFVIIIFc, the formulation of the lyophilized drug product contains [redacted] L-histidine, [redacted] sodium chloride, [redacted] calcium chloride dehydrate, [redacted] sucrose, and [redacted] polysorbate 20, and is the same for all strengths. The prefilled diluent syringe contained 3 mL sterile water for injection for reconstitution of rFVIIIFc prior to administration.

The label will comply with local labeling requirements.

12.1.1. rFVIIIFc Preparation

The individual preparing rFVIIIFc 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. rFVIIIFc Storage

Site stocks of rFVIIIFc 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 with limited access.

12.1.3. rFVIIIFc Handling and Disposal

The Investigator must return all unused vials/kits of rFVIIIFc 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 rFVIIIFc 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. rFVIIIFc 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 rFVIIIFc supplied, dispensed, and subsequently returned to the Sponsor. A written explanation must be provided for any discrepancies.

13. EFFICACY ASSESSMENTS

For future subjects that enroll into ASPIRE, no additional assessments will be added other than those conducted in the parent study.

13.1. Clinical Efficacy Assessments

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

For all subjects:

- Number of bleeding episodes reported by each subject or 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 4-point scale by 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 (see 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 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 rFVIIIFc:

- FVIII activity (determined by one-stage aPTT clotting assay and two-stage chromogenic assay performed at the central laboratory)

- FVIII peak (recovery) and/or trough measurements, if applicable

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 et al, 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 et al, 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 et al, 2011].

HJHS and modified HJHS should only be performed if they were conducted during the parent study.

13.5.2. Patient-Reported 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, they should no longer complete the questionnaire. 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. Parents/guardians will perform these assessments for pediatric subjects 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 et al. 2004]
- Hemo-Sat-Patient Satisfaction Scale for parents/guardians, Version 15 [Mapi Research Institute, 2009]

- CHO-KLAT [CHO-KLAT, 2009]
    - Children, Version 2.0 (for children previously enrolled in study 8HA02PED who are less than 18 years of age).
    - Proxy, Version 2.0p (for parents/guardians of children who were previously enrolled in study 8HA02PED and who are less than 18 years of age)
- EQ-5D-Y [EQ-5D-Y, 2011]
- EQ-5D-3L [EuroQol 1990]

13.5.3. Health Outcomes Related to Hemophilia

Health outcomes will include the following assessments:

- 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 a parent/caregiver

13.5.4. 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 A patient population. This exploratory laboratory assessment consists of DNA testing with full genome sequence.

13.5.5. Archive Plasma Samples

From the volume of blood (approximately 20 mL) taken at each visit, samples for FVIII activity will be collected for each subject at each visit for back-up and archiving. Samples will be archived for testing (if required) for immunologic assays including anti-rFVIIIFc antibodies or further coagulation assays, or for clarification of any clinical or laboratory AE.

14. SAFETY ASSESSMENTS

For future subjects that enroll into ASPIRE, no additional assessments will be added other than those conducted in the parent study.

14.1. Clinical Safety Assessments

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

- Physical examination
- Medical and surgical history (from previous study and updated)
- Height
- Weight
- Concomitant therapy and procedures
- AE and SAE

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 rFVIIIFc:

- 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

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.

15.1.2. Adverse Event

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

Bleeds in this patient population are not considered as AEs. Bleeding episodes that meet a serious criterion (Section 15.1.3) should be reported as an SAE. All bleeding episodes will be captured in the eDiary the subject will be maintaining 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.

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

15.2.3. Serious Adverse Events

Any SAE experienced by the subject between the day of signing the ICF through the last visit is to be recorded on an SAE Form, regardless of the severity of the event or its relationship to study treatment. SAEs must be reported to Quintiles. SAEs that occur up to 21 days after the subject's last dose of rFVIIIFc must also be recorded on the SAE Form eCRF. SAEs must be reported to the designated personnel as detailed in the study file.

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

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

- A subject develops an inhibitor, as defined in Section 7.1.2.
- A Grade 2 or greater allergic drug reaction in association with administration of rFVIIIFc, 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 rFVIIIFc; no parenteral therapy needed
    - Grade 3 Bronchospasm related to rFVIIIFc; parenteral therapy required
    - Grade 4 Anaphylaxis related to rFVIIIFc
- A subject develops a vascular thrombotic event in association with the administration of rFVIIIFc, with the exception of IV injection site thrombophlebitis.

All major surgery should be captured as an SAE.

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 will 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 that the subject has signed the ICF and up to 21 days 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 rechallenge, a reasonable temporal sequence between administration of the drug and the event, a known response pattern of the suspected drug, improvement following discontinuation or dose reduction, a biologically plausible relationship between the drug and the adverse event, or a lack of an alternative explanation for the adverse event.

15.3.2. Severity of Events

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

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

15.3.3. Expectedness of Events

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

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, 100 IU/kg. Overdoses are not considered AEs; however, all overdoses should be recorded on an Overdose Form and faxed to Quintiles Pharmacovigilance within 24 hours. An overdose should be reported even if it does not result in

an AE. Overdoses do not need to be recorded in the eCRF; dosing information is recorded on the eCRF.

15.4.2. Medical Emergency

In a medical emergency requiring immediate attention, study site staff will apply appropriate medical intervention, according to current standards of care. The Investigator or designee should contact the Sponsor Medical Director for this study, Cheryl Pikora, MD, PhD, MPH at +1 781-228-0553 (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. Sponsor Responsibilities

Sponsor'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.
- The Sponsor/designee 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, the data for subjects who enroll from parent studies will be integrated with their data from 8HA01EXT. A parent study is defined as a study where subjects may be enrolled into 8HA01EXT 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(s)

See Section 6.1.1 for a full listing of the study's primary objectives.

16.1.2. Secondary Objective(s)

See Section 6.1.2 for a full listing of the study's secondary objectives.

16.2. Description of Endpoints

16.2.1. Primary Endpoint

See Section 6.2.1 for full descriptions of study endpoints.

16.2.2. Secondary Endpoints

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

16.3. Demography and Baseline Disease Characteristics

The analysis of demography and baseline disease characteristics will be based on the Safety Analysis Set. A description of the Safety Analysis Set is provided in Section 16.6.1.

Demographic 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. Demographic data to be tabulated will include, but not be limited to, age, weight, height, body mass index, ethnicity, and race.

Baseline disease characteristics, based on general medical and surgical, hemophilia, and bleeding histories, will be summarized by 8HA01EXT 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 8HA01EXT will be included in the All-enrolled Analysis Set.

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

16.4.2. General Methods of Analysis

All efficacy endpoints are secondary. No imputation will be applied to any missing efficacy data. For subjects who need/select to have surgeries during the study, their efficacy data during surgical period (including rehabilitation period) will be analyzed separately. The efficacy and surgical/rehabilitation periods will be defined in the statistical analysis plan for the purpose of determining the study periods during which data will be used for select efficacy analyses. Data on bleeding and rFVIIIFc consumption will be based on the efficacy period; surgical evaluations will be based on the surgical/rehabilitation period.

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

16.4.3. Endpoints Analysis

16.4.3.1. Annualized Bleeding Episodes and Annualized rFVIIIFc Consumption

Bleeding episodes will be annualized for each subject first, then summarized and tabulated by treatment arm, treatment regimen, or age cohort, as appropriate, in the parent studies, and by treatment regimen in 8HA01EXT. These analyses will also be performed for each type of bleed (spontaneous and traumatic). The number of spontaneous joint bleeding episodes and the consumption of rFVIIIFc will be annualized in a similar fashion and tabulated.

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 with each response (excellent, good, moderate, no response). These data will be summarized overall and for subgroups of interest 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 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, change from baseline and percent change from baseline, as appropriate.

16.5.2.2. Health Outcomes

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

16.6. Safety

16.6.1. Analysis Population

The Safety Population will include all subjects with at least 1 dose of rFVIIIFc.

16.6.2. Methods of Analysis

For the analysis of safety, data in 8HA01EXT will be integrated with the parent studies, 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 rFVIIIFc 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 deaths. Findings in clinical lab values will be summarized by descriptive statistics. Listings of abnormal laboratory test results will be provided.

The total number of EDs of rFVIIIFc will be summarized by treatment regimen and overall for 8HA01EXT, and overall using combined data from the parent studies and 8HA01EXT.

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

16.8. Optional Laboratory Assessments

Optional laboratory assessment consisting of DNA testing with full genome sequence data may be analyzed to evaluate genetic risk factors in the hemophilia A patient population. The analysis, however, will be in a separate report and will not be included as part of any CSR or interim CSR of 8HA01EXT.

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. The sample size is based on the planned sample sizes of Studies 997HA301 (N=144) and 8HA02PED (N=50), and may be increased based upon subject participation in other rFVIIIFc studies or upon enrollment being greater than expected in studies 997HA301 and/or 8HA02PED.

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 rFVIIIFc while subjects participate in this study (see Section 12). Since study subjects will be required to maintain accurate records of each dose of rFVIIIFc 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 the 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 VIII Fusion Protein (rFVIIIFc) in the Prevention and Treatment of Bleeding Episodes in Previously Treated Subjects with Hemophilia A," Version 3, 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)

22. APPENDIX A: rFVIIIFc DOSING GUIDELINE FOR TREATMENT OF BLEEDING EPISODES

The following table provides guidance for dosing with rFVIIIFc for bleeding episodes. Subjects should consult with the Investigator for an optimal rFVIIIFc level and dosing frequency, but should take only 1 follow-up dose not less than 24 hours after the initial dose. For Major bleeding episodes the subjects will be instructed to administer treatment and contact the study staff as soon as possible.

DOSING GUIDELINES FOR rFVIIIFc THERAPY IN HEMOPHILIA A

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

23. APPENDIX B: HEMOPHILIA JOINT HEALTH SCORE (HJHS)

Appendix B1: Modified HJHS for Subjects Transferring from Study 997HA301

This modified HJHS is based on the scoring system used in a joint scoring reliability study in boys with hemophilia [Hilliard et al., 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 et al., 2011]. This version is for use only with subjects who were previously enrolled in study 997HA301.

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

Pediatric subjects previously enrolled in study 8HA02PED or subjects from any other rFVIIIFc study will continue to use HJHS Version 2.1 (Hemophilia Joint Health Score, Version 2.1, 2011).

24. 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 rFVIIIFc 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. Any bleeding at a different location is considered a separate bleed regardless of time from last injection. Response could also be assessed by the Physician for those subjects who were treated in the hospital with rFVIIIFc for major 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 rFVIIIFc 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

25. APPENDIX D: PHYSICIAN'S GLOBAL ASSESSMENT OF RESPONSE

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

- Excellent: bleeding episodes responded to ≤ the usual number of injections or ≤ the usual dose of rFVIIIFc, 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 require additional agents.

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

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

26. 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 rFVIIIFc treatment using a 4-point clinical scale. This includes observations 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 rFVIIIFc 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 than expected for person without hemophilia **AND**
- No extra doses of rFVIIIFc 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 rFVIIIFc 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

27. APPENDIX F: PATIENT REPORTED OUTCOMES

The following QoL 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 8HA02PED who are less than 18 years of age).
    - Proxy, Version 2.0p (for parents/guardians of children who were previously enrolled in study 8HA02PED and who are less than 18 years of age)
- EQ-5D Y
- EQ-5D 3L